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The prevalence of type 2 diabetes in South Africa: A systematic review

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PREAMBLE

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DECLARATION

I, Carmen Pheiffer, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, or is to submitted for another degree in this or any other university.

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ABSTRACT

The increasing prevalence of type 2 diabetes mellitus (T2DM) poses a major threat to the health and well-being of South Africans. Effective interventions to inform health planning and policy are hampered by the paucity of accurate national epidemiological data. Although several prevalence studies have been conducted, these estimates are not representative of the South African population or are sub-optimal due to the diagnostic methods employed. To address the lack of accurate and representative prevalence data, the aim of this dissertation is to use robust systematic review methods to collate, synthesise and summarise all T2DM prevalence data in South Africa.

The dissertation comprises of four parts. Part A contains the study protocol that was published in *BMJ Open* in 2018. The protocol outlines the problem statement, motivation and rationale, aim, search strategy and robust systematic methods that were used to conduct the study. Part B provides an overview of T2DM enabling a broader understanding of the disease, with a focus on South Africa and the challenges of obtaining accurate T2DM prevalence estimates. We also describe prevention and management strategies for T2DM, and point to priority actions and approaches to achieve such prevention and management of T2DM. Part C consists of a manuscript that has been formatted for submission to *BMJ Open* and Part D is an Appendix with supporting information. This part addresses the aim of the dissertation and presents the systematic review "*The prevalence of type 2 diabetes in South Africa: A systematic review*". The manuscript outlines the rationale and methodologies, together with presenting and discussing the results of the systematic review. Our literature search, which included PubMed, Scopus, Web of Science and African Index Medicus, grey

literature and references of included studies identified 1782 articles published in South Africa between January 1997 and May 2019. Of these, 15 met the inclusion criteria and were included in the systematic review. Heterogeneity across studies did not allow for a meta-analysis and a pooled estimate, thus results are described narratively. Some studies failed to report key methodological elements, which limited our ability to accurately appraise study quality. In conclusion, the systematic review highlights the high prevalence of glucose intolerance in South Africa and confirms the paucity of accurate and representative T2DM prevalence data. There is a need for well-designed epidemiological studies that use best-practice, uniform diagnostic methods to assess prevalence. Collaboration between public health scientists, diabetes specialists and policy makers is recommended to enable the collection of reliable national epidemiological data which can guide policy and planning towards effective diabetes prevention and management strategies.

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Lastly, I would like to thank the lecturing staff at the School of Public Health for equipping me with epidemiological and statistical knowledge, and the skills to conduct this research. Thanks, are also due to the administrative staff for their help in ensuring my documents were submitted on time, especially the late Ms Nazlie Farista, who was always kind, helpful and available to assist.

Thank you.

ABBREVIATIONS

ADA	American Diabetes Association
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
B	Beta
BMI	Body mass index
BODRevMan	Burden of Disease Review Manager
DBS	Dried blood spots
FPG	Fasting plasma glucose
GBD	Global Burden of Disease
GDM	Gestational diabetes mellitus
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	Glycated haemoglobin
HIV	Human immunodeficiency virus
HIV/AIDS	Human immunodeficiency virus/Acquired immunodeficiency syndrome
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGR	Impaired glucose regulation
IGT	Impaired glucose tolerance
LMICs	Low- and middle-income countries
MODY	Maturity onset diabetes of the young
NCD	Non-communicable diseases
OGTT	Oral glucose tolerance test

PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P	Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO	International Prospective Register of Systemic Reviews
SANHANES	South African National Health and Nutrition Examination Survey
SADHS	South African Demographic and Health Survey
SAMRC	South African Medical Research Council
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TB	Tuberculosis
USD	United States Dollars
WHO	World Health Organization

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PART A: PROTOCOL

The prevalence of type 2 diabetes in South Africa: a systematic review protocol

Adapted from**:**

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The formatting and reference style of BMJ Open is adhered to.

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1. ABSTRACT

Introduction

Type 2 diabetes mellitus is a major source of morbidity and mortality in South Africa, spurred by increased urbanisation and unhealthy lifestyle factors. Local epidemiological data are required to inform health planning and policy. The purpose of this systematic review is to identify, collate and synthesise all studies reporting the prevalence of diabetes in South Africa. A secondary aim is to report the prevalence of impaired glucose tolerance and impaired fasting glucose, conditions which are associated with an increased risk of progression to overt diabetes, and the prevalence of undiagnosed diabetes.

Methods and analysis

Multiple databases will be searched for diabetes prevalence studies conducted in South Africa between 1997 and 2018. Two authors will independently select studies that meet the inclusion criteria, extract data and appraise studies using a risk of bias tool for prevalence studies. Studies with low or moderate risk of bias will be included. Sources of heterogeneity will be explored using subgroup analysis.

Ethics and dissemination

The systematic review does not require ethics clearance since published studies with non-identifiable data will be used. This review will provide best estimates to inform the Second National Burden of Disease study which can guide health and policy planning.

PROSPERO registration number: CRD42017071280

2. STRENGTHS AND LIMITATIONS

- The first ever systematic review of type 2 diabetes prevalence in South Africa.
- A comprehensive synthesis of all available diabetes prevalence data in South Africa using a standardised risk of bias tool.
- The protocol adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines.
- The quality of the review will be assessed using the Grading of Recommendations Assessment, Development and Evaluation.
- The heterogeneity in diagnostic criteria, study dates, age of study participants and population groups may limit comparison across studies.

3. INTRODUCTION

Diabetes mellitus, a condition characterised by raised blood glucose levels, is a major source of morbidity, mortality and health costs worldwide. The International Diabetes Federation estimates that in 2017, 451 million adults aged between 20-79 years worldwide had diabetes, with projections of 693 million cases by 2045. Globally, approximately 50% of diabetes cases are undiagnosed, with the majority of these occurring in low-income and middle-income countries. In Africa, the proportion of undiagnosed diabetes is 69.2%. Furthermore, 77% of deaths due to diabetes in Africa occurred in individuals younger than 60 years of age, emphasising the magnitude of the diabetes epidemic, and the urgency to intervene effectively to reduce premature mortality **[1]**. In Africa, as in other parts of the world, type 2 diabetes represents over 90% of diabetes cases **[2,3]**.

The prevalence of diabetes is rapidly increasing in South Africa. In 2009, epidemiological modelling estimated a diabetes prevalence of 9% (2 million) in people aged 30 years and older **[4]**, increasing almost twofold since 2000 when Bradshaw et al estimated a prevalence of 5.5% in the same age group **[5]**. Several factors such as the ageing population, economic transition and urbanisation associated with the nutrition transition and being overweight and/or obese have contributed to the increased diabetes prevalence **[6–9]**. In 2000, it was estimated that 87% of the type 2 diabetes burden in South Africa is attributed to excess body weight **[10]**. This is concerning since in 2013, ~38% of men and ~69% of women in South Africa were considered overweight or obese **[11]**. In 2015, the global burden of disease study estimated that high body mass index and hyperglycaemia, ranked as the second and

third leading risk factors, respectively, after unsafe sex, for early death and disability in South Africa **[12].**

Diabetes, due to its association with several microvascular and macrovascular complications, places a significant burden on the South African health system. In 2009, it was estimated that diabetes caused about 8000 new cases of blindness and 2000 new cases of amputations annually **[4]**. A national burden of disease study in 2000 reported that, among adults 30 years and older, diabetes accounted for approximately 14% of ischaemic heart disease, 10% of stroke, 12% of hypertensive disease and 12% of renal disease burden **[5]**.

Furthermore, the indirect costs of diabetes are high. Diabetes in Africa affects mainly working-aged people between 40 and 60 years of age **[9]**, placing an added burden on the economy due to work absenteeism and decreased productivity. South Africa is battling a quadruple burden of disease due to high rates of infectious diseases, non-communicable disease, maternal and child mortality, and injury-related conditions, thus have limited resources to meet the increased health and economic costs of diabetes **[13]**.

4. RATIONALE

Urgent action is required to halt the burgeoning diabetes epidemic in South Africa. The feasibility of population-level interventions, particularly those aimed at prevention are widely reported **[14]**. However, such initiatives are hampered by the lack of epidemiological data, a challenge faced by all countries in Africa **[15]**. Several studies have measured the prevalence of diabetes in South Africa **[16–26]**, although they were

conducted in different geographical areas (urban vs rural), among different population groups and are generally too small to individually give generalisable prevalence data. Pooling of existing data is considered an effective strategy to generate representative and robust prevalence figures **[8]**. Bertram et al calculated the national prevalence of diabetes in 2009 **[4]**; however, their estimate included only four studies measuring the diabetes prevalence in black South Africans in two rural, one urban and one metro urban population **[21–24]**. The study did not account for population-group variation in diabetes prevalence in South Africa **[16,19,20,23]**, and focused on estimating the disability burden of diabetes rather than characterising the different levels of hyperglycaemia in these populations. This review explores availability and quality of diabetes prevalence data for South Africa.

5. OBJECTIVE

The purpose of this systematic review is to identify, collate and synthesise all studies reporting the prevalence of diabetes in South Africa. A secondary aim is to report the prevalence of impaired glucose tolerance and impaired fasting glucose, conditions which are associated with an increased risk of progression to overt diabetes, and the prevalence of undiagnosed diabetes. These findings will be used to inform the Second National Burden of Disease study which can guide health and policy planning.

6. METHODS

6.1 Study selection

Published population-based surveys, cross-sectional studies and prospective or retrospective cohort studies that report the prevalence of diabetes in South Africa.

6.2 Inclusion criteria

Studies will be included if they were published between January 1997 and February 2018, include more than 100 participants regardless of age, gender, ethnicity, socioeconomic and educational background and study setting, and report the primary outcome using a case definition according to the 1999 WHO diagnostic criteria **[27]**, where type 2 diabetes is diagnosed either by a physician, fasting blood glucose concentrations ≥7.0 mmol/L, 2-hour oral glucose tolerance test values ≥11.1 mmol/L or self-reported use of oral diabetes drugs. In addition, glycated haemoglobin ≥6.5% (48 mmol/mol) will also be used for case definition **[28]**. Due to limitations that hamper the differentiation between type 1 diabetes and type 2 diabetes, diabetes in individuals older than 25 years of age will be classified as type 2 diabetes. Impaired glucose tolerance will be defined by fasting blood glucose concentrations <7.0 mmol/L and 2-hour oral glucose tolerance values ≥7.8 mmol/L, but <11.1 mmol/L. Impaired fasting glucose will be defined as fasting blood glucose concentrations between 6.1 mmol/L and 6.9 mmol/L, and, if available, 2-hour oral glucose tolerance values <7.8 mmol/L **[27]**. Undiagnosed diabetes is defined as the number of new cases of diabetes as a proportion of the total sample.

6.3 Exclusion criteria

Studies will be excluded if they were not conducted in South Africa, do not report the primary outcome, have no clear description of the case definition, and contain data for refugees in camps since they may not be representative of the South African population.

6.4 Primary outcome

Prevalence of type 2 diabetes.

6.5 Secondary outcome

Prevalence of impaired glucose tolerance, impaired fasting glucose and undiagnosed type 2 diabetes.

6.6 Search strategy

A search of articles written in English and indexed in PubMed, Scopus, Web of Science and African Index Medicus between January 1997 and February 2018 will be conducted. An experienced information scientist and disease content experts will be consulted to ensure that the search terms are relevant and optimally arranged, and will include keywords and medical subject headings. An example of the search strategy in PubMed is illustrated in Table 1. The search will be modified to each database. References will be managed in EndNote.

Table 1. *PubMed search strategy*

Search	Query
#4	Search ((#3 NOT (animals[mh] NOT humans[mh]))) AND ("1997/01/01"[Date-Publication] : "2018/02/28"[Date-Publication])
#3	Search (#1 AND #2)
#2	Search (South Africa[mh]OR"South Africa*"[tiab] OR RSA[tiab] OR Africa, Southern[mh:noexp] OR Southern Africa[tiab])
#1	Search (Diabetes[Mesh] OR Diabetes mellitus[Mesh] OR type 2 diabetes mellitus[Mesh] OR type 2 diabetes[Mesh] OR Diabetes mellitus, type 2[Mesh] OR Diabetes, type 2[Mesh] OR hyperglycemia[Mesh] OR blood glucose[Mesh] OR Hemoglobin A, glycosylated[Mesh] OR Glycosylated hemoglobin OR diagnosis OR impaired glucose tolerance OR impaired fasting glucose OR undiagnosed diabetes

6.7 Study selection

The titles and abstracts of articles from the electronic search outputs will be screened independently by two reviewers to identify eligible studies. Disagreements or uncertainties will be resolved by discussion and consensus between the two reviewers, or with a third reviewer if disagreement persists. Full-text copies of the eligible articles will be retrieved and reviewed by two independent reviewers for inclusion. Additional information will be requested from the study authors if required. Reasons for exclusion will be recorded.

6.8 Data extraction

After the final decision to include studies into the review, two authors will independently extract and record data using the Burden of Disease (BOD) Review Manager developed by the Burden of Disease Research Unit of the South African Medical Research Council **[29]**. The following data will be extracted:

- Study details: date of publication, study title, study design, study period and study purpose.
- Study population: province/district of study, study setting (community or health facility based), residential setting (urban or rural) and sample size.
- Response rate.
- Case definition as reported in the study.
- Prevalence of type 2 diabetes, impaired glucose tolerance, impaired fasting glucose and undiagnosed type 2 diabetes.
- Characteristics of study population: age, sex, population group (ethnicity) and comorbid disease (tuberculosis (TB) or human immunodeficiency virus (HIV) status).

After completion, data will be compared and discrepancies will be resolved through consensus between the two reviewers, or in consultation with a third reviewer.

6.9 Risk of bias assessment

Two reviewers will independently appraise the study quality and risk of bias using a checklist for observational epidemiological studies that was adapted from the risk of bias tool for population-based studies **[30]** and the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies **[31,32]**, and standardised in the BOD Review Manager **[29]**. Parameters assessed will include: external validity (whether the

target population is representative of South Africa, representativeness of sample, selection criteria and non-response bias) and internal validity (case definition, validity and reliability of test instruments, consistency of case measurement, appropriateness of time period, and appropriateness of numerators and denominators in estimation). Disagreements between the reviewers over the risk of bias will be resolved by discussion with a third review reviewer where necessary.

6.10 Data synthesis

A narrative description will be conducted for studies with a low or moderate risk of bias. Clinical heterogeneity will be investigated by looking at the characteristics of participants, method of diagnosis and case definitions in the study. Subgroup analyses for study population (province/district, community or health facility based, urban or rural) and characteristics of cases (age, sex, population group, and comorbid disease TB or HIV) will be done if sufficient data exists. If possible, a meta-regression to explore possible sources of variability in prevalence reported between studies will be conducted. Review findings will be displayed using tables and forest plots as appropriate.

6.11 Confidence in cumulative evidence

The strength of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method **[33]**, which scores studies as very low, low, moderate, or high based on methodological flaws within the included studies, consistency of results across diverse studies, precision of estimates and publication bias.

6.12 Patient and public involvement

Patients and the public were not involved.

6.13 Ethics and dissemination

The systematic review does not require ethics clearance since published studies with non-identifiable data will be used. This review is the first to collate and synthesise all the available studies reporting the prevalence of diabetes in South Africa and will provide local epidemiological data to inform the Second National Burden of Disease study, which can guide health and policy planning. Findings from the review will be disseminated in a peer-reviewed journal article and academic reports according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guidelines). The protocol is published adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (Part D-Appendix) **[34]**.

7. AUTHORS' CONTRIBUTIONS

CP, VPvW, JJ and DB conceived the idea and design of the study and drafted the protocol. NL and MN helped to draft the protocol. All authors wrote and approved the final manuscript. CP is the guarantor of the review.

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10. CONFLICT OF INTEREST

The authors have no competing interests.

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PART B: LITERATURE REVIEW

The Harvard reference style is used for Part B, in accordance with university regulations.

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1. INTRODUCTION

Diabetes mellitus is a public health crisis and a significant cause of morbidity and premature mortality decreasing life expectancy by 7-15 years (Ali et al., 2017). In 2017, the International Diabetes Federation (IDF) estimated that 15.5 million people between the ages of 20 and 79 years in sub-Saharan Africa had diabetes. This number is expected to increase to 40.7 million people by 2045 (International Diabetes Federation, 2017). Projections are that sub-Saharan Africa will have the greatest increase globally (International Diabetes Federation, 2017), where the adverse health and economic effects will be devastating. Prevalence and mortality rates of type 2 diabetes mellitus (T2DM), which accounts for over 90% of diabetes cases, have steadily increased in South Africa (Peer et al., 2012; Pillay-van Wyk et al., 2016), a country with an already overburdened and under-resourced health system.

Reliable epidemiological data are important to guide health policy and planning towards developing effective interventions to prevent and manage T2DM. Data modelling have been used to estimate national prevalence (Bradshaw et al., 2007; Bertram et al., 2013), and although these studies used robust methods, their estimates probably underestimate the disease burden due to limitations of the included studies, which were of small size, non-representative and represented an earlier time period. Two national surveys in 2012 (Shisana et al., 2014) and 2016 (National Department of Health et al., 2019) measured T2DM prevalence, however, these were based on self-report and glycated haemoglobin (HbA1c), methodologies with limitations in the South African population (Zemlin et al., 2011; Oni et al., 2017).

The aim of the literature review is to provide an overview of T2DM epidemiology in South Africa, enabling deeper insight into the disease and highlighting the challenges of measuring accurate prevalence data.

2. DIABETES MELLITUS

Diabetes mellitus is a chronic metabolic disease characterised by hyperglycaemia due to defects in insulin secretion, insulin action or a combination of both (Karamanou et al., 2016). Mortality directly attributed to diabetes is listed amongst the top ten causes of deaths globally (WHO, 2017) and in South Africa (Pillay-van Wyk et al., 2016). Furthermore, diabetes is associated with both microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (cardiovascular diseases) complications, increased susceptibility to infections and slow wound healing. In 2015, hyperglycaemia was ranked as the third leading risk factor for death and disability in South Africa (GBD 2015 Risk Factors Collaborators, 2016). Diabetes mellitus is a complex disease with multiple aetiologies, which are broadly divided into different types.

2.1 Type 1 diabetes

Type 1 diabetes mellitus (T1DM), which accounts for approximately 5-10% of diabetes cases worldwide (American Diabetes Association, 2013), occurs due to the failure of pancreatic beta (β) cells to produce insulin and is often diagnosed in younger individuals. Genetic predisposition is considered the major cause of T1DM, although in recent years the role of environmental factors in T1DM aetiology has been suggested (Rewers & Ludvigsson, 2016).

2.2 Type 2 diabetes

Type 2 diabetes mellitus (T2DM) is undeniably the major driver of the diabetes epidemic, accounting for 90-95% of diabetes cases (American Diabetes Association, 2013). It is a complex, progressive disease that primarily occurs due to the inability of the body to respond to insulin, a condition referred to as insulin resistance (Kahn, Hull & Utzschneider, 2006). With time, pancreatic beta (β) cells become dysfunctional, insulin secretion decreases and hepatic glucose production increases leading to postprandial and fasting hyperglycaemia (Figure 1) (Ramlo-Halsted & Edelman, 1999). Complications can manifest up to 10 years before clinical diagnosis, thus the early detection of T2DM is of major importance and greatly researched (Ali et al., 2017).

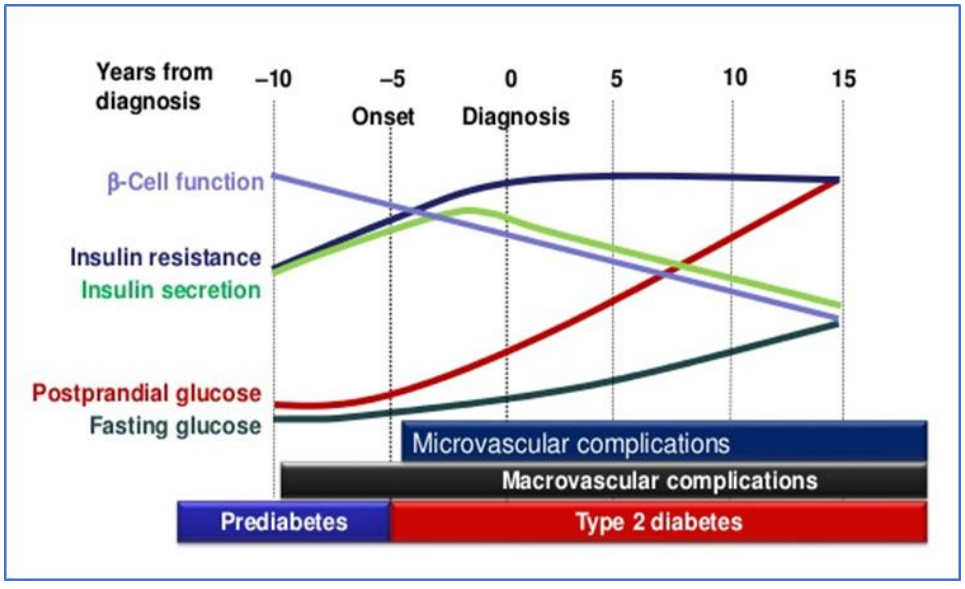

Figure 1. Natural progression of type 2 diabetes. Source: Ramlo-Halsted & Edelman, 1999.

2.3 Other types of diabetes

Gestational diabetes mellitus (GDM), which is defined as hyperglycaemia that is first detected during pregnancy that is not T1DM nor T2DM (World Health Organization, 1999) is receiving renewed interest worldwide, partly due to the increased risk of T2DM in mothers and children (Damm, 2009) and because it presents an ideal opportunity to alter T2DM trajectory (Buyken et al., 2010). It is estimated that up to 14% of pregnancies worldwide are complicated by GDM, although rates vary according to diagnostic criteria and ethnicity (International Diabetes Federation, 2017). Maturity onset diabetes of the young (MODY) is a heterogeneous group of disorders where genetic mutations cause diabetes primarily through their effects on β-cell dysfunction (Gardner & Tai, 2012). Other less common forms of diabetes include genetic defects of insulin action, diseases of the pancreas, and diabetes induced by drugs or infections (American Diabetes Association, 2013).

2.4 Impaired glucose tolerance and impaired fasting glucose

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are commonly referred to as prediabetes (Figure 1) and represent intermediate states of dysregulated glucose homeostasis that precede clinical diagnosis of T2DM (Nathan et al., 2007). Individuals with prediabetes have a 5-12 times higher annual risk of developing T2DM compared to the general population (Gerstein et al., 2007). Different pathophysiological mechanisms underlie prediabetes. IGT is thought to occur due to muscle insulin resistance, IFG due to hepatic insulin resistance, while individuals with both IGT and IFG manifest both muscle and hepatic insulin resistance (Nathan et al., 2007).

3. TYPE 2 DIABETES BURDEN

3.1 Global

A pooled analysis from 751 population-based studies that measured fasting plasma glucose (FPG) concentrations and included 4,372,000 adults from 146 countries, reported that the global age-standardised T2DM prevalence in adults 18 years and older increased from 5.0% in 1980 to 7.9% in 2014 in females and 4.3% to 9.0% in males (NCD Risk Factor Collaboration, 2016). This prevalence is similar to the 8.8% prevalence estimated by the IDF, albeit their estimates were calculated from studies that included self-report, medical records, different age ranges (i.e. 18 years and older compared to 20-79 years as reported by IDF) and/or biomarkers (International Diabetes Federation, 2017). Deaths due to T2DM increased by 43.0%, largely due to population growth and ageing, while age-standardised death rates increased by 5.9% between 2007 and 2017 (Roth et al., 2018). Global health expenditure on people with diabetes aged 20-79 years is estimated at 727 billion USD (United States Dollars), increasing more than 3-fold since 2007 (International Diabetes Federation, 2017). Similarly, indirect costs due to decreased productivity and economic activity, and societal costs are high. Although historically considered a disease of developed nations, urbanisation and demographic and epidemiological transition have increased the burden of T2DM in low- and middle- income countries (LMICs) also.

3.2 Africa

The IDF estimates that the prevalence of T2DM in Africa will increase more than 2.6-fold over the next 25 years, the highest projected increase of T2DM globally (International Diabetes Federation, 2017). It is estimated that 69.2% of diabetes cases in Africa are undiagnosed, reflecting low awareness, inadequacies in health systems

and limited access to care. Approximately 80% of diabetes deaths in Africa occur in the economically active group (individuals younger than 60 years of age), thus diabetes is a significant cause of indirect economic (decreased productivity due to absenteeism and suboptimal work performance) and intangible (psychosocial harm) costs.

3.3 South Africa

South Africa is ranked as an upper-middle income country (World Bank, 2014) and the second largest economy in Africa. Despite this, it is plagued by high economic and health inequalities due to years of racial and gender discriminatory policies, which have led to a sub-optimal health system with health outcomes often worse than those in poorer countries (Coovadia et al., 2009). South Africa has a unique quadruple disease burden characterised by high rates of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) and Tuberculosis (TB), non-communicable diseases, maternal and childhood mortality, and injury-related disorders (Mayosi et al., 2009). Epidemiological modelling demonstrated that the prevalence of T2DM has almost doubled from 5.5% in 2000 to 9% in 2009 (Bradshaw et al., 2007; Bertram et al., 2013). More recent studies, although not nationally representative, report an age-adjusted prevalence of 13.1% (Peer et al., 2012) or 26.3% (Erasmus et al., 2012) depending on population group. Furthermore, these studies report a high prevalence of IGT and undiagnosed diabetes (11.2% and 4.9%, respectively (Peer et al., 2012) and 15.3% and 18.1%, respectively (Erasmus et al., 2012)), indicating a high overall burden of glucose intolerance. A community-based study reported that the prevalence of T2DM and IGT increased approximately 60% between 1990 and 2008/2009 (Peer et al., 2012), while national diabetes mortality rates increased by 29% between 1997 and 2012 (Pillay-van Wyk et al., 2016). This increase is most probably continuing, as risk factors of T2DM have significantly increased in recent years. Furthermore, T2DM increases the risk for microvascular and macrovascular complications. In 2009, it was estimated that diabetes accounted for about 8000 new cases of blindness and 2000 new cases of amputations annually in South Africa (Bertram et al., 2013), while 14% of ischaemic heart disease, 10% of

stroke, 12% of hypertensive disease and 12% of renal disease in South Africa was attributed to diabetes in 2000 (Bradshaw et al., 2007).

3.3.1 Type 2 diabetes risk factors

Both modifiable and non-modifiable risk factors for T2DM such as obesity and ageing have increased in sub-Saharan Africa (Peer et al., 2014; Atun et al., 2017), with urbanisation and population ageing arguably the biggest culprits. Urbanisation is associated with the adoption of unhealthy lifestyles characterised by energy-dense diets and physical inactivity. South Africans are considered to be among the most overweight and obese people globally, with 69% of women and 39% of men overweight or obese (Ng et al., 2014), while 87% of T2DM cases in South Africa are attributable to excess body weight (Joubert et al., 2007). A study conducted in black Africans about 30 years ago, reported that urbanisation is associated with a 2.3-fold increased likelihood of developing diabetes (Levitt et al., 1993). Alarmingly, urbanisation rates for this population group has steadily increased since then (Kok and Collinson, 2006). Population ageing, due to the improvement in health systems and access to care, increases the total burden of T2DM in the population (Peer et al., 2014). Other risk factors include genetics (Yako et al., 2016), population group self-identified as “Indian” (Shisana et al., 2014; National Department of Health et al., 2019), female gender (Peer et al., 2012; Hilawe et al., 2013), sedentary lifestyles, harmful alcohol consumption, low levels of education, impaired psychological state and selected socio-cultural factors (Peer et al., 2012, 2014; Duncan et al., 2014).

3.3.2 Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome and Tuberculosis

The impact of HIV/AIDS and TB on the T2DM epidemic in South Africa, a country with a high prevalence of these infectious diseases is concerning (Human Sciences Research Council, 2018). The widespread implementation and success of antiretroviral treatment (ART) programmes and TB treatment have significantly increased life expectancy of those living with HIV/AIDS and TB and contributed to population ageing and risk for T2DM (Rehle et al., 2015; Non, Escota & Powderly, 2017). Moreover, interactions between these infectious diseases and T2DM exacerbate each other. Both HIV infection and ART is associated with premature ageing and metabolic dysfunction (Lagathu et al., 2017) and increases T2DM risk (Non, Escota & Powderly, 2017; Pepin et al., 2018), while interactions between diabetes and TB are common and exacerbate disease burden (Noubiap et al., 2019).

4. TYPE 2 DIABETES DIAGNOSIS

Diagnostic criteria for T2DM have evolved over the last few decades, although measurement of glucose concentrations has remained the cornerstone (Polonsky, 2012). Glucose concentrations are measured in whole blood, serum or plasma, with venous plasma recommended by the National Academy of Clinical Biochemistry and the American Diabetes Association (ADA) (Sacks et al., 2002, 2011) and the most commonly used method. The diagnostic criteria are illustrated in Table 1, although the preferred test and the one best able to predict long-term microvascular and macrovascular disease is still not conclusive (World Health Organization, 2006, 2011; American Diabetes Association, 2013). Clinical diagnosis of diabetes requires two abnormal glucose measurements or one abnormal glucose measurement in the

presence of symptoms such as increased thirst and urine production, blurring of vision and weight lost. Acute infections, trauma and stress may lead to transient hyperglycaemia; thus, an additional confirmatory test is required for asymptomatic individuals (Alberti & Zimmet, 1998).

4.1 Oral glucose tolerance test

The oral glucose tolerance test (OGTT) measures glucose concentrations two hours after ingestion of a 75-g glucose load following an eight-hour fast. The OGTT is the gold standard for T2DM diagnosis and is the only test able to detect impaired insulin function, the major pathophysiology of T2DM (Cox & Edelman, 2009). The OGTT is resource-intensive in terms of health care personnel, costs, time, necessity of fasting and requires an additional clinic visit to obtain results, limiting its use. In some instances, the OGTT has shown poor reproducibility due to intra-individual heterogeneity (Mooy et al., 1996; Ko et al., 1998).

4.2 Fasting plasma glucose

The FPG test measures glucose concentrations after fasting for at least eight hours and is the most commonly used test due to pragmatic reasons. Although, more convenient and less time consuming than the OGTT, measuring FPG still requires overnight fasting, a return clinic visit to obtain results, and has poor sensitivity compared to OGTT (Cox & Edelman, 2009), probably reflecting different disease pathophysiology.

4.3 Glycated haemoglobin

In 2009 the ADA recommended the use of glycated haemoglobin (HbA1c) as an alternative diagnostic test, which was later adopted by the World Health Organization (WHO) (International Expert Committee, 2009; World Health Organization, 2011). Glycated haemoglobin is formed by the binding of glucose to haemoglobin and reflects glycaemic control over a three-month period. The HbA1c test is gaining popularity since it can be conducted in a non-fasted state, is less time consuming than the OGTT and is a good indicator of chronic hyperglycaemia and long-term complications. However, the accuracy of the test is affected by ethnicity, haemoglobinopathies, red blood cell disorders and anaemia (Zemlin et al., 2011).

Table 1. *Type 2 diabetes diagnostic criteria*

	WHO criteria	ADA criteria
Type 2 diabetes Fasting plasma glucose Two-hour OGTT glucose HbA1c	 ≥ 7.0 mmol/L ≥ 11.1 mmol/L ≥ 6.5 % (48 mmol/L)	 ≥ 7.0 mmol/L ≥ 11.1 mmol/L ≥ 6.5 % (48 mmol/L)
Impaired glucose tolerance* Fasting plasma glucose Two-hour OGTT glucose HbA1c	 < 7.0 mmol/L ≥ 7.8 & < 11.1 mmol/L N/A	Fasting: ≥ 5.6 & < 7.0 mmol/L Two-hour: ≥ 7.8 & < 11.1 mmol/L HbA1c: 5.7 - 6.4 %
Impaired fasting glucose* Fasting plasma glucose Two-hour OGTT glucose HbA1c	 ≥ 6.1 & < 7.0 mmol/L < 7.8 mmol/L N/A	

*Impaired glucose tolerance and impaired fasting glucose are referred to as prediabetes by the American Diabetes Association.

HbA1c, Glycated haemoglobin; OGTT, Oral Glucose Tolerance Test

(World Health Organization, 1999, 2011; American Diabetes Association, 2013)

4.4 Point-of-Care diagnosis

In recent years, point-of-care testing has attracted interest for the diagnosis of T2DM due to its many advantages, which include convenience, use of fingerprick blood, immediate results and decision-making without the need for repeated visits (Vučić Lovrenčić et al., 2013). Although several studies have reported that point-of-care tests offer potential, their clinical applicability has not been satisfactorily demonstrated and measurement of glucose concentrations in an accredited laboratory is still recommended by the National Academy of Clinical Biochemistry and the ADA (Sacks et al., 2011).

4.5 Dried blood spots

Dried blood spots (DBS), which are obtained by allowing a few drops of capillary blood collected via finger prick to absorb onto filter paper, have garnered interest as an alternative to venous blood for HbA1c testing (Affan et al., 2014). Attaining DBS is more cost effective and acceptable to study participants, safer, requires less training of staff and is logistically easier to store and transport than venous blood. Studies comparing DBS to venous blood samples have shown the potential of DBS to serve as a proxy for venous blood, although lack of standardisation of sample collection, transportation, storage and analysis, prevent its clinical use at present (Affan et al., 2014; Mastronardi et al., 2015).

4.6 Challenges of measuring type 2 diabetes prevalence

The complex pathophysiology of T2DM, together with the variation in diagnostic methods and criteria, negatively impacts the ability to accurately assess the prevalence of T2DM (Danaei et al., 2015). These inadequacies, which are particularly

evident in sub-Saharan Africa, contribute to the inaccuracy of global T2DM estimates and the lack of an estimate on the “true” burden of T2DM. Organisations such as the NCD Risk Factor Collaboration, IDF and GBD calculate global estimates based on data pooled from country-specific prevalence data, which are often lacking or of poor quality. To obtain estimates for countries without prevalence data, the IDF extrapolates data from other nations with similar characteristics (such as demography), although some of these extrapolations are inappropriate due to ethnic and socio-economic reasons (Zimmet et al., 2016). The validity of global T2DM estimates is further hampered by the challenges of measuring prevalence, which include misdiagnosis due to measurement error of diagnostic tests, and sampling and reporting bias as illustrated in Table 2. Alarmingly, these national and global estimates are confidently used by the scientific community for reporting and decision-making. Furthermore, there is a paucity of estimates on IGT, largely due to challenges of the OGTT, the only test able to diagnose IGT. IGT is a significant predictor of future T2DM thus these estimates are critical to assess the total burden of glucose intolerance and for implementing effective interventions (Gerstein et al., 2007). Using OGTT, although considered more accurate to detect diabetes cases, may reduce response rate, hence increase sampling bias, especially in large-scale surveys. This is one of the main considerations for recommending FPG or HbA1c for surveillance.

Table 2. *Challenges of measuring type 2 diabetes prevalence in epidemiological studies*

Challenge	Reason
Measurement error (sensitivity, accuracy and reliability of diagnostic tests)	
Non-standardisation of diagnostic method	Studies use different diagnostic tests with different sensitivities and specificities (Danaei et al., 2015; Kengne et al., 2017), reflecting the complexity and multiple pathophysiologies of T2DM.
Poor performance of FPG compared to OGTT	FPG misses a significant number of diabetes cases compared to OGTT (Werfalli et al., 2016; Kengne et al., 2017). This has important ramifications for global diabetes monitoring since the WHO STEPWise approach to surveillance (STEPS) recommends using FPG (WHO, n.d.).
Poor performance of HbA1c compared to OGTT	The performance of the test is affected by ethnicity and haemoglobinopathies, which are common in Africa. The development of population-specific cut-offs is required (Zemlin et al., 2011).
Incorrect cut-offs	The application of incorrect cut-offs may underestimate or overinflate the prevalence of T2DM (Taylor et al., 2016), with important ramifications for global diabetes monitoring (Bennett et al., 2017; Ezzati et al., 2017).
Pre-analytical and analytical variation	Quality assurance is not applied to many epidemiological studies, while delays in sampling handling, plasma separation and measurements could affect diagnosis due to the instability of glucose in blood samples (Alberti & Zimmet, 1998; Zimmet et al., 2016).
Non-fasted state	The OGTT and FPG requires fasting prior to testing. Fasting is difficult to measure and poses a limitation, particularly in epidemiology surveys where participants may not be as committed to fasting as in a clinical setting (Maimela et al., 2016; Zimmet et al., 2016).
Self-report	Accuracy of self-report ranges between 64% to 98% in developed countries. In Africa, these are expected to be lower due to high rates of undiagnosed diabetes and stigmatisation (Margolis et al., 2008; Peer et al., 2014).
Error due to sampling and reporting bias	
Inaccurate estimates	Sampling bias due to convenience and non-random sampling, age-related demographical factors, etc. (Atun et al., 2017).
Transient hyperglycaemia	Diabetes is diagnosed using a single abnormal glucose measurement, thus transient hyperglycaemia due to other conditions may incorrectly be diagnosed as T2DM (Alberti & Zimmet, 1998).

5. PREVENTION AND MANAGEMENT OF TYPE 2 DIABETES

5.1 Prevention of type 2 diabetes

The health and economic costs of preventing T2DM are considerably more favourable than managing the disease and its complications (Ali et al., 2017). Interventions targeting modifiable risk factors are effective. Improving diet and physical activity have been shown to prevent T2DM (Knowler et al., 2002; Unwin & Alberti, 2006), particularly in high risk groups (IGT and IFG) (Orozco et al., 2008). We eagerly await the results of a lifestyle intervention study conducted in Pretoria, South Africa (Pengpid, Peltzer & Skaal, 2014) to determine whether simple population-level interventions aimed at improving health literacy, raising public awareness about the signs and symptoms of T2DM and promoting healthier lifestyles are able to prevent T2DM in South Africa.

5.2 Lifestyle interventions to treat type 2 diabetes

Lifestyle modification is the recommended first-line treatment for newly diagnosed patients (Lakhtakia, 2013). This involves increasing awareness about T2DM risk factors and educating patients about the importance of a healthy diet, physical activity and the harmful effects of smoking and alcohol abuse. Well-structured educational programs for both health care providers and patients have shown success in controlling T2DM (Ali et al., 2017). Unfortunately, lifestyle modifications are difficult to adhere to because of the high costs of healthy eating, barriers to physical activity and stresses of life, which increase reliance on pharmacological drugs.

5.3 Pharmacological management

Several classes of antidiabetic drugs are available for treating T2DM. Metformin monotherapy is the recommended first-line antidiabetic treatment. Other drugs (Sulphonylureas, Meglitinides, Alpha-glucosidase inhibitors, Thiazolidinediones, Dipeptidyl peptidase-4 inhibitors, Sodium glucose co-transporter-2 inhibitors, injectable GLP-1 agonists and Insulin) are prescribed when metformin effectivity wanes or due to adverse effects (Marín-Peñalver et al., 2016). In South Africa, health inequalities cause disparities in the availability, accessibility and affordability of diabetes medication. Medicines are often not available leading to poor health outcomes. A study in an urban community in the Western Cape reported that only 38.6% of people with T2DM were on treatment, and of these, only 25.5% had fasting glucose values < 6.0 mmol/L (Peer et al., 2012). The situation is likely to be worse in rural settings and in other provinces due to decreased access to care. Uncontrolled diabetes is associated with increased risk of complications (Ali et al., 2017). Health systems strengthening using locally developed interventions such as 'Quality Circles', which aim to integrate health care providers, health care systems, communities and patients and their families (Maimela et al., 2018), are critical to improve the management T2DM and improve health outcomes.

5.4 Effective and cost-effective interventions

The Delphi process, a forecasting method based on responses from a panel of experts, was used to rank interventions to prevent and manage diabetes in LMICs (Ali et al., 2017). Prevention and management interventions that were recommended include blood pressure control among people with diabetes, which was considered a high priority and found most feasible and very cost-effective (Ali et al., 2017). Care

management to support risk factor control and lifestyle interventions to prevent diabetes among high risk individuals were also considered highly effective and cost-effective. Lifestyle interventions are likely to offer the greatest long-term likelihood to slow the growth of diabetes globally, however, implementing them are challenging. To achieve these interventions, the following priority actions and approaches were recommended: a) targeted screening to detect persons with prediabetes and diabetes, espoused in guidelines and policy, and ensuring that the health system has adequate capacity to handle the concomitant health needs of such detection; b) facilitation of physical and financial access to essential medication to treat diabetes and vascular risks in diabetes, as well as access to laboratory testing for monitoring related markers; c) prevention and care services in clinical and non-clinical settings, such as community halls and work places, by non-clinical staff such as lifestyle coaches or community health workers; and d) research to address key knowledge and best-practice gaps, including standardised measurements, and why certain interventions work and others are not considered effective and cost-effective (Ali et al., 2017).

In South Africa, early detection of retinopathy and appropriate management can prevent blindness (Hofman, Cook & Levitt, 2014). Further, these authors showed that screening using a mobile retinal camera is highly cost-effective, with its costs and follow-up treatment being less than the expense of a one-year disability grant. In 2017, Priceless SA, a research unit in the School of Public Health at the University of Witwatersrand provided evidence that fiscal measures such as taxation of sugary drinks is a cost-effective method with potential to decrease the health burden of T2DM in South Africa (Priceless SA, 2017).

6. SYSTEMATIC REVIEWS

Systematic reviews are at the apex in the hierarchy of epidemiological studies and is considered the best available evidence for decision-making (Mallett et al., 2012). The review process involves a systematic, transparent and predefined method of data collection and study appraisal. Results are synthesised as a meta-analysis, depending on the heterogeneity between included studies, or may be described narratively. Although systematic reviews were originally developed to evaluate interventions, they have been adapted to assess observational studies with the concomitant adaptation of tools to appraise studies (Hoy et al., 2012; Murad et al., 2017). Despite their increased popularity, the systematic review process may be flawed by poor design and execution of the review process. Although these may be overcome, reviews have fundamental limitations due to the quality of included studies, lack of raw data and reliance on author's self-report (Mallett et al., 2012; Møller, Ioannidis & Darmon, 2018). Despite these disadvantages, a well-conducted systematic review may be useful to identify gaps in knowledge and highlight methodological inconsistencies and weaknesses.

7. CONCLUSION

The literature review has provided an overview of T2DM, briefly describing the different types of diabetes and the burden globally and in Africa and South Africa. I highlighted risk factors in South Africa and listed the challenges of measuring T2DM prevalence in epidemiological studies. Lastly, I described prevention and management strategies for T2DM, and pointed to priority actions and approaches to achieve such prevention and management of T2DM. Type 2 diabetes is an escalating public health crisis, particularly in South Africa, due to health inequalities and the already overburdened

and under-resourced health system. Moreover, given the country's population growth, population ageing, and little success in preventing obesity at the population level (National Department of Health, 2019), the most important risk factor for T2DM (NCD Risk Factor Collaboration, 2016), such escalation seems inevitable. Urgent and effective population-level interventions are required to delay the onset or prevent T2DM. In addition, a strong drive in primary care to identify all people at high risk of developing T2DM with available and reliable measures, together with available and effective drug supply, such as metformin, and providing advice and take-home information towards inducing and maintaining changes in lifestyle (NCD Risk Factor Collaboration, 2016), may be an interim approach until effective population-level interventions deliver successful detection, prevention and management of T2DM. Such initiatives in South Africa, however, are hampered by the lack of recent and reliable national prevalence data to inform health policy and planning. There is an urgent need for representative epidemiological data on the prevalence of T2DM in South Africa. To address the paucity in national T2DM prevalence data in South Africa, it would be valuable to undertake a systematic review to identify, appraise, collate and synthesise all studies that report T2DM prevalence. Such a review has not been undertaken previously, and Part C and D of this thesis address this need.

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PART C: MANUSCRIPT

Prevalence of type 2 diabetes in South Africa: a systematic review

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1. ABSTRACT

Objectives The aim of this study was to estimate the prevalence of type 2 diabetes mellitus (T2DM), impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and undiagnosed T2DM in South Africa.

Study design Systematic review of studies reporting T2DM prevalence in South Africa published between January 1997 and May 2019. PubMed, Scopus, Web of Science and African Index Medicus, grey literature and references of included studies were searched. Two reviewers independently selected studies and the quality of included studies was appraised using a web-based system, the Burden of Disease Review Manager (BODRevMan) adapted from the risk of bias tool for population-based studies and the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies.

Setting All studies conducted in South Africa irrespective of geographical location.

Participants All South Africans irrespective of population group, age and gender.

Outcomes The primary outcome was prevalence of T2DM. The secondary outcomes were IGT, IFG and undiagnosed T2DM.

Results A total of 1782 articles were identified, 1651 titles and abstracts were screened for eligibility, full-text articles requested for 55, of which 15 were included in the study. Heterogeneity across studies did not allow for a meta-analysis and a pooled estimate, thus results are described narratively. Some studies failed to report key methodological elements, which limited our ability to accurately appraise study quality.

Conclusions We report a high prevalence of glucose intolerance in South Africa. Moreover, we highlight the paucity of nationally representative T2DM prevalence data, and the need for well-designed epidemiological studies that use best-practice, uniform diagnostic methods to assess prevalence. Collaboration between public health

scientists, diabetes specialists and policy makers are essential to enable the collection of reliable national epidemiological data which can guide policy and planning towards diabetes prevention and management strategies.

PROSPERO registration number: CRD42017071280

Keywords

Prevalence, South Africa, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting glucose, undiagnosed diabetes

2. STRENGTHS AND LIMITATIONS

- The first systematic review of type 2 diabetes mellitus (T2DM), impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and undiagnosed T2DM prevalence in South Africa.
- A comprehensive synthesis of all available T2DM prevalence data in South Africa using rigorous systematic review methods, standardised risk of bias tools and adhering to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.
- Inadequate reporting of methods limited risk of bias and quality assessment of studies, while choice of study population limited generalisability of the findings.
- Gaps in diagnostics for T2DM may result in over- or underestimation of prevalence.
- Heterogeneity across studies did not allow a meta-analysis for a pooled estimate, nor the analyses and description of trends over time.

3. INTRODUCTION

Diabetes affects approximately 451 million adults worldwide, with projections of 693 million cases by 2045 [1]. The largest increase is predicted for Africa where in 2017, 15.5 million adults had diabetes, with 69.2% of people unaware of their diabetic status. Africa is already grappling with high rates of infectious diseases thus diabetes poses a serious health and economic burden to these already overburdened and under-resourced health systems [1]. To achieve the United Nations Sustainable Development Goal 3, which aims to reduce premature mortality from non-communicable diseases (NCDs) by a third by 2030 [2], requires urgent action and effective intervention strategies to combat the rising diabetes epidemic in Africa. In Africa, as in other parts of the world, type 2 diabetes mellitus (T2DM) represents over 90% of diabetes cases [3].

South Africa is ranked as an upper-middle income country [4] and is the second largest economy in Africa. Despite this, it is plagued by high economic and health inequalities due to years of racial and gender discriminatory policies, which have led to a sub-optimal health system with health outcomes often worse than those in poorer countries [5]. South Africa has a unique quadruple disease burden characterised by high rates of Human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS) and Tuberculosis (TB), non-communicable diseases, maternal and childhood mortality, and injury-related disorders [6]. The prevalence of T2DM has almost doubled from 5.5% in 2000 to 9% in 2009 [7,8], and although these estimates were based on robust modelling methods, they probably underestimate the current disease burden as risk factors of T2DM have significantly increased in recent years. Rapid urbanisation characterised by the adoption of unhealthy energy-dense diets and

physical inactivity have contributed to the steadily increasing obesity epidemic, with 69% of women and 39% of men in South Africa being overweight or obese [9]. Excess bodyweight is estimated to account for 87% of T2DM cases in South Africa [10], while HIV/AIDS and antiretroviral treatment (ART) is associated with premature ageing, metabolic dysfunction, increased life expectancy and risk for T2DM [11–15]. It is estimated that a staggering 20% of people between 15 and 64 years of age in South Africa are HIV infected [16]. Recent studies estimate the T2DM age-adjusted prevalence at 13.1% [17] or 26.3% [18] depending on population group. Furthermore, high rates of glucose intolerance, which is associated with a 5-12 times higher annual risk of developing T2DM compared to the general population [19], and undiagnosed diabetes have been reported [17,18], demonstrating a high overall burden of dysglycaemia. Mortality directly attributable to diabetes, increased by 29% between 1997 and 2012 [20], this increase most probably continuing. In 2009, it was estimated that diabetes accounted for about 8000 new cases of blindness and 2000 new cases of amputations annually in South Africa [8], while 14% of ischaemic heart disease, 10% of stroke, 12% of hypertensive disease and 12% of renal disease in South Africa is attributed to diabetes [7].

Reliable national epidemiological data on T2DM prevalence are required to inform health policy and planning to facilitate appropriate prevention and management strategies. Two national surveys have been conducted [21,22], however methodological concerns about these studies (sub-optimal response rates and diagnostic tests) and the lack of generalisable data from research studies [17,18,23–28] prompted this review. The aim of this systematic review is to estimate the T2DM prevalence in South Africa between 1997 and 2018. The prevalence of IGT, IFG and

undiagnosed diabetes will also be assessed to estimate the overall prevalence of glucose intolerance in South Africa. This data could inform policy and planning for prevention and management of T2DM.

4. METHODS

This systematic review was conducted adhering to the published protocol [29] and is registered with the Prospective Register of Systemic Reviews (PROSPERO): CRD42017071280. The review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Part D-Appendix) [30].

4.1 Literature Search

Four major databases (PubMed, Scopus, Web of Science and African Index Medicus) were searched for studies on the prevalence of T2DM in South Africa, published between January 1997 and May 2019. These databases were selected as they were comprehensive, indexing articles from several disciplines from notable journals, and grey literature such as theses/dissertations, technical reports, etc. that contain information specific to Africa [31]. Search terms included keywords and medical subject headings (MeSH) such as diabetes mellitus, T2DM, glycosylated haemoglobin, diagnosis, IGT, IFG and undiagnosed diabetes including corresponding synonyms and associated terms for each item. The search strategy is shown in Supplementary Table 1 (Part D-Appendix) and was adapted for each database, and references were managed in EndNote X7.0.1 (Thomson Reuters). Reference lists of eligible studies were searched to identify studies for possible inclusion; we contacted experts in the field to identify further potentially eligible studies.

4.2 Eligibility criteria

Population-based surveys, cross-sectional studies and prospective or retrospective cohort studies were included if they were conducted in South Africa and had more than 100 participants regardless of gender, population group [32], age, socioeconomic and educational background, and reported the primary outcome (T2DM prevalence) according to World Health Organization (WHO) diagnostic criteria [33–35]. Population group was classified according to previously defined apartheid categories of Black African, Coloured, Indian/Asian, White and other, which was introduced into the new birth death notification in 1998 to track health inequalities [32]. Only individuals aged 25 years and older were included for T2DM prevalence.

4.3 Outcome measures

Primary outcome:

T2DM defined as fasting plasma glucose (FPG) ≥7.0 mmol/L, 2-hour oral glucose tolerance test (OGTT) plasma glucose ≥11.1 mmol/L, glycated haemoglobin (HbA1c) ≥6.5% (48 mmol/mol) or self-reported use of oral diabetes drugs.

Secondary outcomes:

IGT (FPG <7.0 mmol/L and 2-hour OGTT plasma ≥7.8 mmol/L and <11.1 mmol/L), IFG (>6.1 mmol/L and < 7.0 mmol/L); and

Undiagnosed T2DM defined as the number of new cases of diabetes as a proportion of the total sample [34,35,35].

4.4 Study selection, quality assessment and data extraction

After removal of duplicates, two reviewers (CP, VPvW or ET) independently screened titles and abstracts to select full-text articles for inclusion. The two reviewers assessed

each included study for risk of bias using a web-based standardised checklist for systematic review of observational epidemiological studies, Burden of Disease Review Manager (BODRevMan) developed by the South African Medical Research Council [31], that was adapted from the risk of bias tool for population-based studies [36] and the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies [37,38] (Supplementary Table 2, Part D-Appendix). Two authors independently extracted and recorded data using BODRevMan. Data extracted included date of publication and details of study design, location, population characteristics, response rates, T2DM, IGT, IFG and undiagnosed T2DM prevalence, and case definition as reported in the study. When not reported, depending on the study design, and if the necessary information was available 95% Confidence Intervals (95% CI) were calculated in STATA® version 14.0 (StataCorp, College Station, TX, USA). For national surveys (South African National Health and Nutrition Examination Survey (SANHANES) and South African Demographic Health Survey (SADHS)), data were reanalysed taking design effect into consideration. Comorbid disease (HIV/AIDS and TB) was documented when reported. Corresponding authors were contacted when further clarification/more information was required. Raw data from studies and national surveys were recalculated to only include prevalence in individuals 25 years and older. Disagreements or uncertainties at each stage of the review process (screening, risk of bias assessment and data extraction) were resolved by discussion and consensus between the two reviewers, or with a third reviewer if disagreement persisted (CP, VPvW or ET).

4.5 Data synthesis and analysis

Clinical heterogeneity was explored by looking at the characteristics of participants, method of diagnosis and case definitions in the study. A meta-analysis nor meta-regression were possible due to extensive heterogeneity of included studies with respect to population group, study design and geographical location. Thus, a narrative synthesis of the included studies was conducted. Studies were too diverse to undertake a meaningful subgroup analysis. Results are displayed using tables and forest plots (Excel, Microsoft Office 15) as appropriate.

4.6 Confidence in cumulative evidence

The strength of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method [39,40], which scores studies as very low, low, moderate, or high based on methodological flaws within the included studies, consistency of results across diverse studies, precision of estimates and publication bias.

4.7 Patient and public involvement

Patient and public were not involved in the study.

5. RESULTS

5.1 Selected studies

Figure 1 displays the flow diagram for the review process. A total of 1782 articles were identified with 1651 records left after removal of duplicates. Titles and abstracts were screened for eligibility, after which 55 were selected for full-text review, of which 15 studies met the inclusion criteria and were included in the systematic review. Studies were conducted between 1997 and 2016, and in different population groups, provinces, locations (urban vs. rural), age groups and using different diagnostic tests (FPG, OGTT or HbA1c) according to WHO criteria [33–35]. The studies included two national surveys SANHANES and SADHS, and 10 community- and 3 facility-based research studies. The national surveys included all population groups, eight studies were conducted in Black Africans, three were conducted in Coloureds, one in Indians and one study was conducted in a population consisting of both Black African and Coloured individuals. Most studies were conducted in urban settings (six urban, two peri-urban, four rural and three studies were conducted in both urban and rural settings). The ages of participants across studies varied to include those between certain age bands only, or everyone aged 15 and above. Raw data from these studies were recalculated to only include those aged 25 years and older. Study characteristics are listed in Supplementary Table 3 (Part D-Appendix). In most studies reporting was sub-optimal, which limited risk assessment. Furthermore, a few studies did not report the data in the required format or failed to report 95% CIs. Authors were contacted and numbers were recalculated to obtain usable data and 95% CIs.

5.2 Type 2 diabetes prevalence

Studies that report the prevalence of T2DM are presented in Figure 2. Although some studies reported age-adjusted prevalence, the crude prevalence was used in the forest plot to facilitate comparability between studies. The prevalence of T2DM ranged from 3.0% to 35.2% according to population group, age, geographic location and diagnostic test. A high prevalence of T2DM was reported in Indians (35.2% [43]) and Coloureds (28.2% [18], 19.3% [41] and 24.6% [42]). The prevalence of T2DM in Black Africans ranged from 3.0% in a small study conducted amongst factory workers in the Eastern Cape [25] to 12.1% [17] and 16.5% [44] in urban populations from the Western Cape and KwaZulu Natal, respectively. SANHANES reported a prevalence of 14.7% [22] and SADHS a prevalence of 14.9% [21]. A higher prevalence was reported in rural compared to urban settings in the Free State (7.9% vs. 4.3% [45]) (Supplementary Table 3). It was not possible to compare diagnostic test across the 15 studies since they were conducted in different population groups, ages and settings. However, two studies compared the performance of different diagnostic tests (Supplementary Table 4, Part D-Appendix) [44,46]. Hird et al. [44] reported a similar prevalence irrespective whether FPG (11.8%), OGTT (10.3%) or HbA1c (12.9%) was used, whereas Oni et al [46] reported a higher prevalence of T2DM and impaired glucose regulation using HbA1c (8.2% and 39.5%) compared to FPG (4.1% and 10.6%) and OGTT (3.3% and 10.6%). These higher rates of diagnosis using HbA1c was particularly evident in TB positive individuals [46]. Eight studies reported T2DM prevalence estimates for females and males (Figure 3). Prevalence was consistently higher in females compared to males, although the increase in two studies were small [25,26]. Seven studies reported T2DM prevalence across different age groups. As expected, all

studies reported that prevalence increased with age (Figure 4), with an extremely high prevalence (59.8%) observed in Indians between 55 and 64 years of age [43].

5.3 Impaired glucose tolerance, impaired fasting glucose and undiagnosed diabetes

The prevalence of IGT and IFG mirrored T2DM (Figure 5A), with the highest rates reported in Indians and Coloureds [18,42,43]. Comparatively lower rates were reported in Black Africans (0.9%-10.7%) [17,25,26,44,46], although a high prevalence (20.3%) was reported in Black African females in an urban community [47]. The prevalence of undiagnosed T2DM ranged from 2.7% to 18.1% (Figure 5B). The highest prevalence (18.1%) was observed in Coloureds [18].

5.4 Tuberculosis/Human immunodeficiency virus

Although not representative, prevalence data for studies conducted during TB and HIV comorbidity were included for informative purposes and are illustrated in Figure 6. Two studies, which were both conducted in rural settings in Limpopo reported a prevalence of 4.5% in HIV positive [48] and 12.5% HIV negative [49] individuals, although the former was conducted in a health centre, while the latter was community based. One study, which was conducted in a TB clinic in the Western Cape reported T2DM prevalence in both HIV negative and positive individuals [46]. Prevalence of T2DM was higher in HIV negative (16.0%) compared to HIV positive (8.9%) individuals, and in TB positive (12.6%) compared to TB negative (10.1%) patients (Figure 6, Supplementary Table 3, Part D-Appendix).

5.5 Publication bias

We attempted to minimise publication bias in this review in a number of ways. A comprehensive search, which included consulting with experts to identify grey or unpublished literature was conducted. Four major databases were searched [31]. Reference lists of articles were screened to identify potentially eligible studies. At least two review authors independently scrutinised and selected articles for inclusion in the review using pre-specified eligibility criteria, assessed risk of bias and extracted data.

5.6 GRADE

The overall level of evidence as qualified with GRADE was low as shown in Supplementary Table 5 (Part D-Appendix) due to limitations in study design, poor response rate, unclear risk of bias, methodological limitations, more studies reporting on female population creating gender bias which negatively affects generalisability and wide confidence intervals.

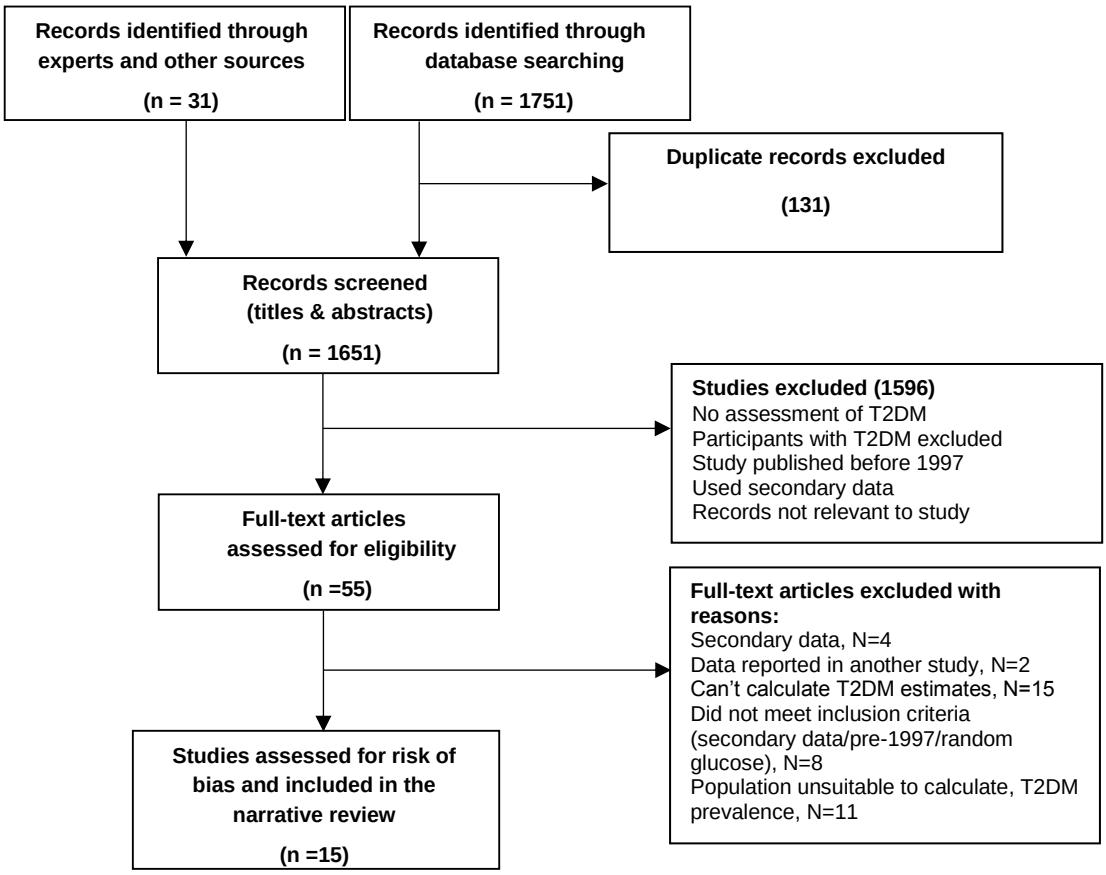


Figure 1. Flow diagram showing selection of studies for inclusion in the systematic review.

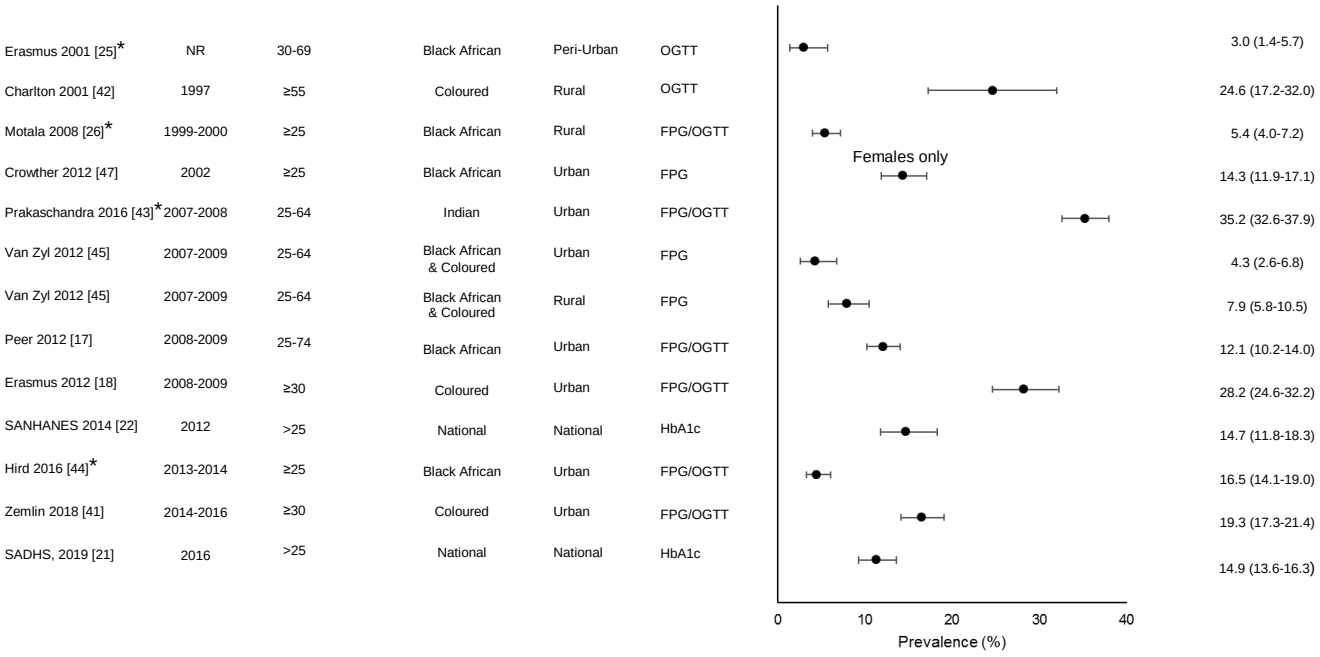


Figure 2. Forest plot of type 2 diabetes prevalence.

Note: Data are represented as the crude prevalence and 95% CI. Prevalence was measured in females (Crowther et al. 2012 [47]) only. *Data were recalculated to include individuals 25 years and older.

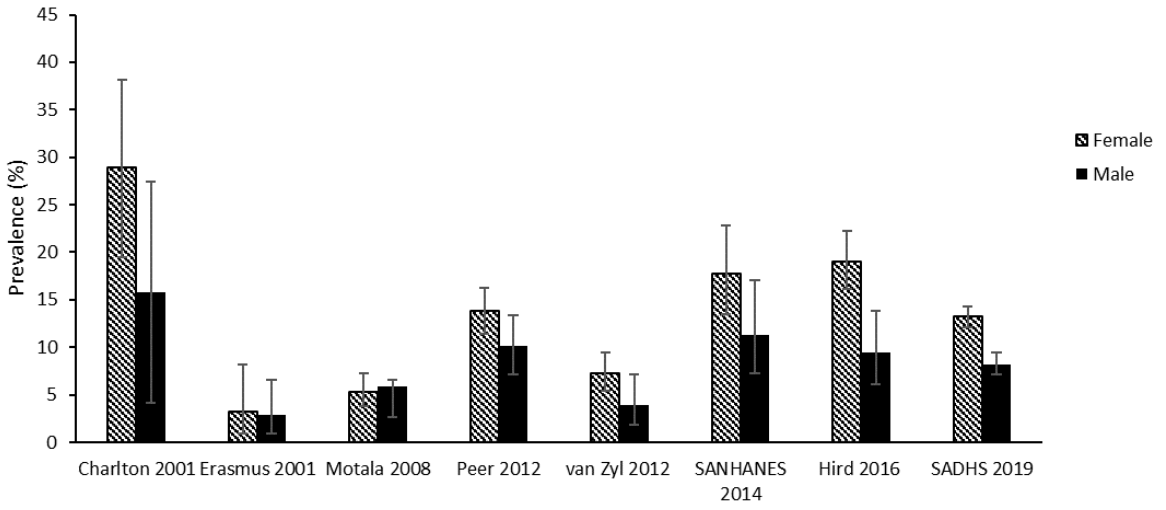


Figure 3. Prevalence of type 2 diabetes in females and males.

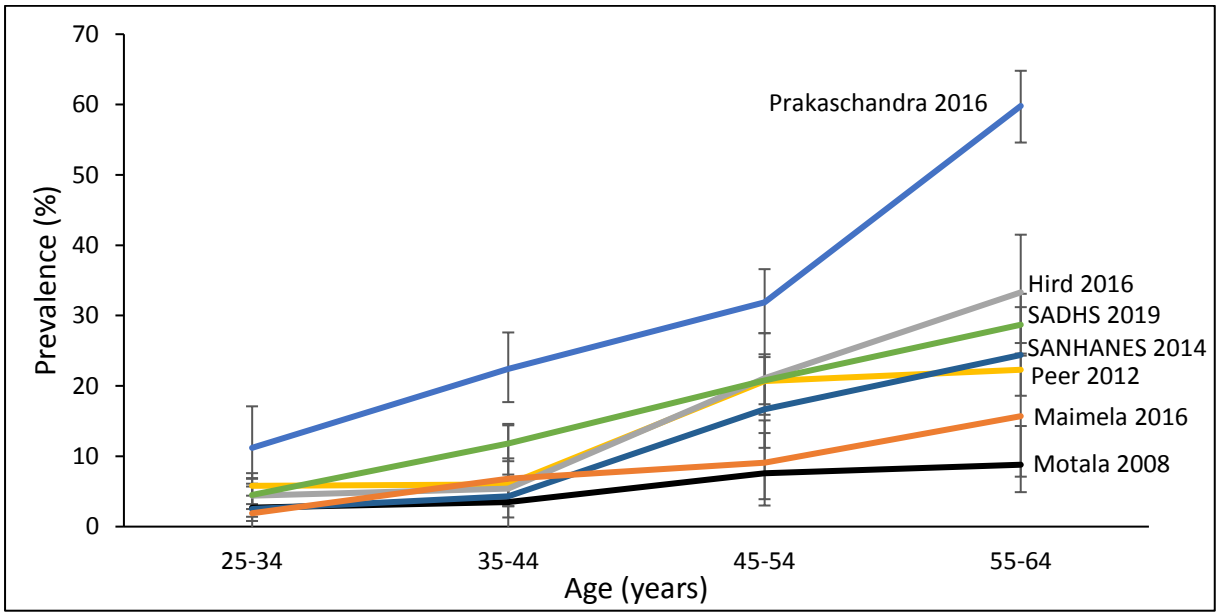
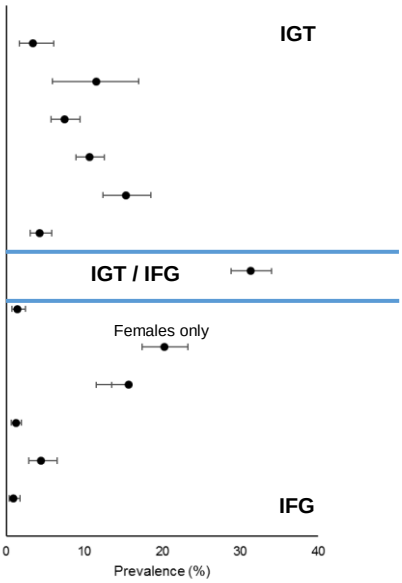


Figure 4. Prevalence of type 2 diabetes across different age bands.

A

Author	Year	Age (years)	Population group	Location	Diagnostic test	Prevalence (95% CI)
Erasmus 2001 [25]*	NR	30-69	Black African	Peri-Urban	OGTT	3.4 (1.6-6.1)
Charlton 2001 [42]	1997	≥55	Coloured	Rural	OGTT	11.5 (5.9-17.0)
Motala 2008 [26]*	1999-2000	≥25	Black African	Rural	FPG/OGTT	7.5 (5.8-9.4)
Peer 2012 [17]	2008-2009	25-74	Black African	Urban	FPG/OGTT	10.7 (8.9-12.6)
Erasmus 2012 [18]	2008-2009	≥30	Coloured	Urban	FPG/OGTT	15.3 (12.4-18.5)
Hird 2016 [44]*	2013-2014	≥25	Black African	Urban	FPG/OGTT	4.3 (3.1-5.8)
Prakaschandra 2016 [43]*	2007-2008	25-64	Indian	Urban	FPG/OGTT	31.4 (28.8-34.0)
Motala 2008 [26]*	1999-2000	≥25	Black African	Rural	FPG/OGTT	1.4 (0.7-2.5)
Crowther 2012 [47]	2002	≥25	Black African	Urban	FPG/OGTT	20.3 (17.4-23.3)
Prakaschandra 2016 [43]*	2007-2008	25-64	Indian	Urban	FPG/OGTT	15.6 (13.7-17.8)
Peer 2012 [17]	2008-2009	25-74	Black African	Urban	FPG/OGTT	1.2 (0.6-1.9)
Erasmus 2012 [18]	2008-2009	≥30	Coloured	Urban	FPG/OGTT	4.4 (2.9-6.5)
Hird 2016 [44]*	2013-2014	≥25	Black African	Urban	FPG/OGTT	0.9 (0.4-1.7)



B

Author	Year	Age (years)	Population group	Location	Diagnostic test	Prevalence (95% CI)
Erasmus 2001 [25]*	NR	30-69	Black African	Peri-Urban	OGTT	2.7 (1.2-5.3)
Motala 2008 [26]*	1999-2000	≥25	Black African	Rural	OGTT	4.6 (3.3-6.3)
Peer 2012 [17]	2008-2009	25-74	Black African	Urban	OGTT	4.9 (3.6-6.3)
Erasmus 2012 [18]	2008-2009	≥30	Coloured	Urban	FPG/OGTT	18.1 (15.0-21.6)
Zemlin 2018 [41]	2014-2016	≥30	Coloured	Urban	FPG/OGTT	6.4 (5.2-7.7)

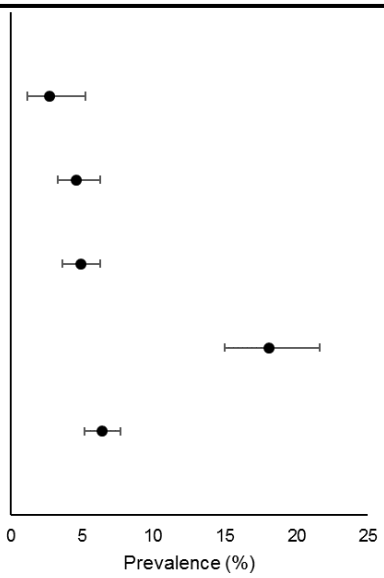


Figure 5. Forest plot of impaired glucose tolerance and impaired fasting glucose (A) and undiagnosed diabetes (B).

Note: Prevalence was measured in females (Crowther et al. 2012 [47]) only. *Data were recalculated to include individuals 25 years and older.

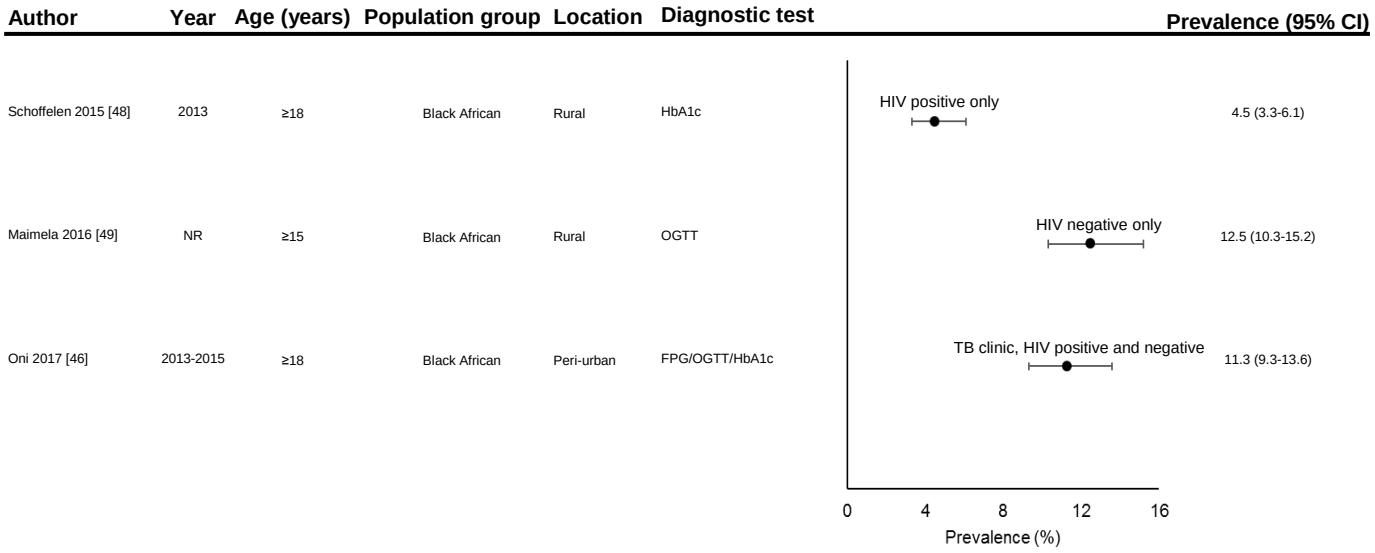


Figure 6. Forest plot of type 2 diabetes prevalence in TB and HIV studies.

6. DISCUSSION

This systematic review shows that the prevalence of T2DM in South Africa varies according to population group, age, gender, diagnostic test and comorbid disease, highlighting the challenges of measuring T2DM prevalence [50]. The heterogeneity of studies did not allow for a meta-analysis to calculate a pooled estimate or do a trend analysis. Nonetheless, we provide compelling evidence that glucose intolerance (T2DM, IGT, IFG and undiagnosed T2DM) in South Africa is high and poses a significant threat to the already overburdened and under-resourced health system.

The greatest source of heterogeneity in T2DM prevalence was population group and reflects NCD mortality rates, which are highest for Indians, followed by Coloureds and lowest in Black Africans [20]. Black Africans and Coloureds are confronted with the highest dual burden of NCDs and infectious disease, while mortality in Indians and Whites are mainly due to NCDs [20]. Population group differentials are postulated to be due to “the legacy of Apartheid and the state of health transition”. These differences could be ascribed to socio-economic status and/or genetics. Differences in insulin resistance, the main pathophysiology of T2DM, have been reported between Black African and White South African women [51,52], while Indians may be genetically predisposed to T2DM through innate susceptibilities in β-cell dysfunction [53].

The positive correlation between age and T2DM prevalence is consistent with scientific evidence linking increasing age with progressive glucose intolerance [54]. Demographic transition and population ageing due to the widespread implementation and success of ART regimens and improvements in access to care [14,15], will thus undeniably increase the prevalence of T2DM and burden on our health system. In

2015, a systematic review on diabetes prevalence in Africa reported an overall prevalence of 13.7% amongst individuals aged 55 years and older [38]. Alarmingly, most of the studies in South Africa report an almost two-fold higher prevalence in this age group [17,21,22,42,44]. Rapid urbanisation and adoption of unhealthy lifestyles are considered major drivers of the T2DM epidemic [38]. Urban/rural disparities were not markedly apparent in our review and are consistent with findings from urban and rural communities in South Africa and Zambia [55]. Rates of modifiable risk factors (obesity, physical activity and smoking) in rural communities are high [56] and could partly account for the high prevalence of T2DM in these communities. The prevalence of T2DM in females was higher than in males, possibly due to increased insulin resistance [57] and obesity [9] in South African women compared to their male counterparts. Furthermore, gender bias could have affected results since most studies had more female than male participants, a common caveat in epidemiological studies. The WHO has recently recommended gender-based interventions against NCDs [58], signifying the importance of gender disparities in disease.

Diagnosis of T2DM is contentious, with no single preferred diagnostic test. The OGTT, which measures glucose concentrations two hours after ingesting 75-g of glucose is considered the gold standard for T2DM diagnosis, however, is cumbersome to perform. The FPG and HbA1c tests are often employed as diagnostic tests in place of the OGTT depending on health care facility and resources [59]. The two included studies that compared diagnostic tests, showed no significant difference between OGTT and FPG [44,46], in contrast to previous studies from South Africa [26,42,59], Africa [38] and globally [60] that report that the use of FPG alone misses a significant number of diabetes cases, and motivates for the use of OGTT. Differences between

the OGTT and FPG test may reflect population differences due to disease stage and pathophysiology, thus both tests are recommended. Importantly, OGTT is the only test able to detect IGT, the major pathophysiology associated with T2DM and essential to estimate overall burden of glucose intolerance. Discrepancies between diagnostic tests were mainly evident when measuring HbA1c, particularly in TB patients [46]. The HbA1c test also fared poorly in a large international pooled analysis of population-based health surveys [48], and physiological differences related to red blood cell turnover (anaemia and iron status) has been suggested to contribute to regional variations. Thus, although the test does not require fasting and is clinically more convenient and acceptable to patients, poor sensitivity and false positivity in TB patients limit its use in South Africa. Studies to identify appropriate HbA1c cut-offs in South Africa [59] or develop novel diagnostic tests that are applicable to our population [63–66] are required.

The prevalence of T2DM was lower in HIV negative compared HIV positive individuals, in contrast to the widely held view that HIV infection and ART treatment increases the risk for T2DM [12,13]. Similar findings were reported in other studies in South Africa [55,67], and are thought to be due to decreased adiposity during HIV infection or improved health awareness as part of ART programs. Alternatively, HIV infection could increase disease severity resulting in early mortality, which would translate to decreased prevalence. This hypothesis requires further exploration.

In conclusion, we report a high prevalence of glucose intolerance in South Africa. Moreover, we highlight the heterogeneity of T2DM prevalence across population group, age, gender, setting, diagnostic test, and HIV/AIDS and TB status, which all

contribute to the challenges of measuring prevalence and the paucity of nationally representative T2DM prevalence data. Well-designed epidemiological studies that use best-practice, uniform diagnostic methods to assess prevalence are urgently required. Collaboration between public health scientists, diabetes specialists and policy makers are essential to enable the collection of reliable national epidemiological data to guide policy and planning towards facilitating appropriate diabetes prevention and management strategies. Political commitment is essential to prioritise and allocate resources to alter the trajectory of T2DM.

7. AUTHORS' CONTRIBUTIONS

CP, VPvW, JJ and DB conceived the idea and design of the study. CP, VPvW and ET conducted the systematic review and drafted the manuscript. All authors contributed intellectual input, and reviewed and approved the final draft. CP is the guarantor of the review.

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9. CONFLICT OF INTEREST

The authors have no competing interests.

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PART D: APPENDICES

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Supplementary Table 1. *PubMed search strategy*

Search	Query
#4	Search ((#3 NOT (animals[mh] NOT humans[mh]))) AND ("1997/01/01"[Date-Publication] : "2019/05/28"[Date-Publication])
#3	Search (#1 AND #2)
#2	Search (South Africa[mh]OR"South Africa*"[tiab] OR RSA[tiab] OR Africa, Southern[mh:noexp] OR Southern Africa[tiab])
#1	Search (Diabetes[Mesh] OR Diabetes mellitus[Mesh] OR type 2 diabetes mellitus[Mesh] OR type 2 diabetes[Mesh] OR Diabetes mellitus, type 2[Mesh] OR Diabetes, type 2[Mesh] OR hyperglycemia[Mesh] OR blood glucose[Mesh] OR Hemoglobin A, glycosylated[Mesh] OR Glycosylated hemoglobin OR diagnosis OR impaired glucose tolerance OR impaired fasting glucose OR undiagnosed diabetes

The PubMed search strategy was adapted for optimal searching in the other databases.

Supplementary Table 2. *Quality assessment criteria for prevalence studies*

Domain	Criteria	Question	Score
External validity	Representativeness	Was a sample size calculation conducted and is it adequate?	1
		Is the target population a close representation of the national population in relation to relevant variables?	1
		Was the sampling frame a true or close representation of the population?	1
		Was a form of random selection used to select the sample? Was the sampling method appropriate for the research question?	2
	Non-response bias	Were there similarities between participants and non-participants in relation to demographic characteristics?	1
		Was the overall/response rate of the study reported?	1
		What was the overall/response rate for the study?	1
		Was the overall/response rate adequate for the study? Excellent ≥80%, Average 60-79%, Poor <60%	1
Internal validity	Case definition	Were the cases classified using the ICD codes or was an acceptable case definition used? What is the case definition?	1
		Were the study instruments used to measure the parameter of interest shown to have reliability and validity in this study or a previous study?	2
	Data collection	Were data collected directly from the participants or is a proxy was used, was it appropriate?	1
		Was the same mode of date collection used for all participants for the condition of interest?	1
	Uncertainty of estimation	Was the parameter of interest reported with uncertainty, i.e. Standard deviation (SD), Standard Error (SE) or 95% Confidence Interval (CI)?	1
	Appropriateness of time factor for outcome measure	Was the length of recall period for the parameter of interest appropriate to ascertain outcome/exposure?	2
	Appropriateness of numerator and denominator in calculation of estimate	Were the numerator and the denominator for the parameter of interest appropriate? If not, can these be extracted to recalculate the parameter of interest?	2
	Confounding	Were potential confounding factors sought and controlled for?	1
		Total Score	20

Risk of bias was assessed using a web-based standardised checklist for systematic review of observational epidemiological studies, Burden of Disease Review Manager (BODRevMan) developed by the South African Medical Research Council [31], that was adapted from the risk of bias tool for population-based studies [36] and the Newcastle-Ottawa Scale for assessing the quality of non-randomised studies [37,38].

Supplementary Table 3. *Characteristics of included studies*

Authors and Year	Sampling	Population Group[1]	Date	Province	Location	Diagnostic criteria	Age (years)	N[2]	Test	Condition	Prevalence (95% CI)			Risk Score
											Total	**Females**	**Males**	
Charlton 2001 [42]	Convenience	Coloured	1997	WC	Rural	WHO, 1985	≥55	129	OGTT	T2DM	24.6 (17.2-32.0)	28.9 (19.5-38.2)	15.8 (4.2-27.4)	**14**
										IGT	11.5 (5.9-17.0)	10 (3.8-16.2)	13.2 (2.4-24.0)	
Erasmus 2001 [25]	Convenience (factory workers)	Black African	NR	EC	Peri-Urban	WHO, 1985	20-69	374	OGTT	T2DM	2.4 (1.1-4.5)	2.9 (0.8-7.3)	2.1 (0.7-4.9)	**11**
										Age-adjusted	4.5 (1.5-7.4)	-	-	
										T2DM (>=30 years)	3.0 (1.4-5.7)	3.3 (0.9-8.2)	2.9 (0.9-6.6)	
										20-29 years	0	0	0	
										30-39 years	0	0	0	
										40-49 years	4.8 (1.8-10.2)	3.4 (0.4-11.7)	6.1 (1.7-14.8)	
										50-59 years	8.1 (1.7-21.9)	18.2 (2.3-51.8)	3.8 (1.0-19.6)	
										>=60 years	0	0	0	
										IGT-OGTT	2.7 (1.3-4.9)	1.5 (0.2-5.2)	3.4 (1.5-6.5)	
										Age-adjusted	5.1 (2.4-5.5)	-	-	
										IGT (>=30 years)	1.6 (6.1-3.4)	-	-	
										20-29 years	0	0	0	
										30-39 years	3.1 (0.9-7.7)	3.8 (0.5-13.2)	2.6 (0.3-9.1)	
										40-49 years	4.0 (1.3-9.1)	0	7.6 (2.5-16.8)	
										50-59 years	0	0	0	
										>=60 years	20 (0.5-71.6)	0	20 (0.5-71.6)	
										Undiagnosed (>=30 years)	2.1 (0.9-4.2) 2.7 (1.2-5.3)	-	-	
Motala 2008 [26]	Random cluster	Black African	1999-2000.	KZN	Rural	WHO,1998	≥15	999	FPG/OGTT	T2DM	4.6 (3.4-6.1)	4.6 (3.3-6.3)	4.5 (2.1-8.4)	**16**
										Age-adjusted	3.9 (2.8-5.3)	3.9 (2.7-5.5)	3.5 (1.4-7.1)	
										T2DM (>=25 years)	5.4 (4.0-7.2)	5.4 (3.8-7.3)	5.8 (2.7-6.6)	
										15-24 years	0	0	0	
										25-34 years	2.7 (0.8-6.9)	3.2 (0.9-7.9)	0	
										35-44 years	3.5 (1.3-7.4)	4.0 (1.5-8.4)	0	
										45-54 years	7.6 (3.9-13.3)	7.1 (3.1-13.5)	9.7 (2.0-25.8)	
										55-64 years	8.8 (4.9-14.3)	7.7 (3.8-13.7)	13.8 (3.9-31.7)	
										>=65 years	5.0 (2.5-8.7)	5.4 (2.5-9.9)	3.9 (0.5-13.2)	
										IGT	6.4 (5.0-8.1)	6.4 (5.0-8.1)	6.5 (3.5-10.9)	
										Age-adjusted	4.8 (3.6-6.3)	4.7 (3.6-6.3)	4.6 (2.4-9.0)	
										IGT (>=25 years)	7.5 (5.8-9.4)	-	-	
										15-24 years	0.7 (0-3.6)	0.9 (0.2-5.1)	0	
										25-34 years	2.7 (0.8-6.9)	3.2 (0.9-7.9)	0	
										35-44 years	5.2 (2.4-9.6)	5.3 (2.3-10.2)	4.6 (0.1-22.8)	
										45-54 years	5.6 (2.4-10.7)	3.5 (1.0-8.8)	12.9 (3.6-29.8)	

										55-64 years	8.8 (4.9-14.3)	10.0 (5.4-16.5)	3.5 (0.09-17.8)	
										>=65 years	12.7 (8.6-17.8)	12.5 (7.9-18.4)	5.8 (1.2-15.9)	
										IFG	1.6 (0.9-2.6)	0.9 (0.4-1.8)	4.5 (2.1-8.4)	
										Age-adjusted	1.5 (0.8-2.5)	0.8 (0.3-.6)	4.0 (1.7-7.8)	
										IFG (>=25 years)	1.4 (0.7-2.5)	-	-	
										15-24 years	2.6 (0.7-6.5)	1.9 (0.2-6.5)	4.4 (0.5-14.8)	
										25-34 years	0	0	0	
										35-44 years	1.2 (0.1-4.1)	0.7 (0-3.6)	4.6 (0.1-22.8)	
										45-54 years	2.1 (0.4-6.0)	0	9.7 (2.0-25.8)	
										55-64 years	1.3 (0.2-4.5)	1.5 (0.2-5.4)	0	
										>=65 years	1.8 (0.5-4.6)	0.6 (0-3.3)	5.8 (1.2-15.9)	
										Undiagnosed	3.9 (2.8-5.3)	NR	NR	
										(>=25 years)	4.6 (3.3-6.3)	-	-	
van Zyl 2012 [45]	Stratified proportional cluster	Black African & Coloured	2007-2009	FS	Urban and Rural	WHO, 1998	25-64	955	FPG	T2DM-Urban	4.3 (2.6-6.8)	5.1 (2.9-8.1)	2.1 (0.3-7.3)	**14**
										T2DM-Rural	7.9 (5.8-10.5)	9.1 (6.4-12.4)	5.0 (2.2-9.6)	
Peer 2012[3] [17]	Multistage cluster	Black African	2008-2009	WC	Urban	WHO, 1998	25-74	1071	FPG/OGTT	T2DM	12.1 (10.2-14.0)	13.8 (11.4-16.3)	10.2 (7.1–13.4)	**18**
										Age-adjusted	13.1 (11.0-15.1)	14.7 (12.1-17.3)	11.3 (8.0-14.6)	
										25-34 years	5.8	NR	NR	
										35-44 years	6	NR	NR	
										45-54 years	20.7	NR	NR	
										55-64 years	22.3	NR	NR	
										>=65 years	38.6	NR	NR	
										IGT	10.7 (8.9-12.6)	NR	NR	
										Age adjusted	11.2 (9.2-13.1)	NR	NR	
										25-34 years	5	NR	NR	
										35-44 years	9.7	NR	NR	
										45-54 years	18.6	NR	NR	
										55-64 years	16.9	NR	NR	
										>=65 years	19.9	NR	NR	
										IFG	1.2 (0.6-1.9)	NR	NR	
										Age adjusted	1.2 (0.6-1.9)	NR	NR	
										25-34 years	0.8	NR	NR	
										35-44 years	2.2	NR	NR	
										45-54 years	1.3	NR	NR	
										55-64 years	0.8	NR	NR	
										>=65 years	1.1	NR	NR	
										Undiagnosed	4.9 (3.6-6.3)	4.9 (0.9-7.1)	4.8 (0.9-6.9)	
Erasmus 2012 [18]	Stratified random	Coloured	2008-2009	WC	Urban	WHO, 1998	≥30	642	FPG/OGTT	T2DM	28.2 (24.6-32.2)	NR	NR	**16**
										Age-adjusted	26.3 (22.0-30.3)	NR	NR	
										IGT	15.3 (12.4-18.5)	NR	NR	
										Age-adjusted	15.0 (11.4-18.6)	NR	NR	
										30-39 years	14.3 (7.4-24.1)	13.8 (6.5-24.7)	16.7 (2.1-48.4)	

										40-49 years	12.1 (7.9-17.5)	11.9 (7.4-18.0)	12.8 (4.3-27.4)	
										50-59 years	18.5 (13.1-25.0)	20.4 (14.0-28.2)	12.2 (4.1-26.2)	
										>=60 years	16.4 (10.0-24.6)	14.0 (7.7-22.7)	29.4 (10.3-56.0)	
										IFG	4.4 (2.9-6.5)	NR	NR	
										Age-adjusted	3.2 (1.6-4.9)	NR	NR	
										30-39 years	6.5 (2.1-14.5)	6.2 (1.7-15.0)	8.3 (0.2-38.5)	
										40-49 years	5.1 (2.4-9.1)	5.0 (2.2-9.7)	5.1 (0.6-17.3)	
										50-59 years	4.5 (2.0-8.7)	5.1 (2.1-10.2)	2.4 (0.1-12.9)	
										>=60 years	1.8 (0.2-6.4)	2.2 (0.3-7.6)	0	
										Undiagnosed	18.1 (15.0-21.6)	NR	NR	
										Age-adjusted	16.8 (13.3-20.4)	NR	NR	
										30-39 years	6.5 (2.1-14.5)	7.7 (2.5-17.0)	0	
										40-49 years	14.7 (10.0-20.4)	15.7 (10.4-22.3)	20.5 (9.3-36.5)	
										50-59 years	16.8 (11.7-23.2)	19.7 (13.4-27.4)	17.1 (7.2-32.1)	
										>=60 years	28.2 (20.0-37.6)	31.2 (22.0-41.6)	11.8 (1.5-36.4)	
Crowther 2012[4] [47]	Volunteer	Black African	2002	Gauteng	Urban	WHO, 1998	≥18	746	FPG	T2DM	14.3 (11.9-17.1)	14.3 (11.9-17.1)		**12**
										IFG	20.3 (17.4-23.3)	20.3 (17.4-23.3)		
SANHANES 2014 [22]	Multistage cluster	All South Africans	2012	National	Urban and Rural	WHO, 2011	>25	1063	HbA1c	T2DM	14.7 (11.8-18.3)	17.7 (13.5-22.8)	11.3 (7.3-17.0)	**18**
										25-34 years	2.5 (1.4-4.4)			
										35-44 years	4.3 (2.9-6.4)			
										45-54 years	16.7 (11.2-24.1)			
										55-64 years	24.4 (18.6-31.2)			
										>=65 years	19.0 (15.7-22.8)			
Schoffelen 2015[5] [48]	Random, facility-based HIV-positive patients	Black African	2013	Limpopo	Rural	WHO, 2011	≥ 18	904	HbA1c	T2DM	4.5 (3.3-6.1)			
Prakaschandra 2016 [43]	Two-stage cluster	Indian	2007-2008	KZN	Urban	WHO, 2005	15-64	1378	FPG-T2DM OGTT -IGT	T2DM	27.4 (25.0-29.8)	29.4 (26.6-32.3)	21.5 (17.4-26.0)	**16**
										Age-adjusted	20.1 (18.0-22.3)			
										T2DM (>=25 years)	35.2 (32.6-37.9)			
										15-24 years	6.1 (2.7-11.7)			
										25-34 years	11.2 (6.8-17.1)			
										35-44 years	22.4 (17.7-27.6)			
										45-54 years	31.9 (27.5-36.6)			
										55-64 years	59.8 (54.6-64.8)			
										IFG	14.4 (12.6-16.3)	15.1 (13.0-17.6)	12.2 (9.1-15.9)	
										Age-adjusted	8.0 (6.6-9.5)			
										IFG (>=25 years)	15.6 (13.7-17.8)			
										15-24 years	2.3 (0.5-6.5)			
										25-34 years	4.9 (2.2-9.6)			
										35-44 years	9.8 (6.7-13.8)			
										45-54 years	19.6 (15.9-23.7)			
										55-64 years	20.4 (16.4-24.9)			
										IGT/IFG	29.1 (26.7-31.6)	31.8 (28.9-34.8)	22.0 (17.9-6.5)	

										Age-adjusted IGT/IFG (>=25 y) 15-24 years 25-34 years 35-44 years 45-54 years 55-64 years	17.6 (15.7-19.8) 31.4 (28.8-34.0) 7.6 (3.7-13.6) 19.9 (14.0-26.9) 27.1 (22.1-32.6) 38.7 (34.1-43.6) 31.3 (26.5-36.3)			
Hird 2016 [44]	Multistage cluster	Black African	2013-2014	KZN	Urban	WHO, 1998, 2011	≥ 18	1190	FPG/OGTT	T2DM Age-adjusted T2DM (>=25 years) 15-24 years 25-34 years 35-44 years 45-54 years 55-64 years >=65 years IGT Age-adjusted IGT (>=25 years) 15-24 years 25-34 years 35-44 years 45-54 years 55-64 years >=65 years IFG Age-adjusted IFG (>=25 years) 15-24 years 25-34 years 35-44 years 45-54 years 55-64 years >=65 years	12.6 (10.8-14.6) 12.9 (11.0-14.9) 14.1 (19.0-16.5) 0.4 (0.05-2.5) 4.4 (2.5-7.6) 5.4 (2.9-9.7) 21.1 (15.9-27.5) 33.3 (26.1-41.5) 34.9 (26.1-41.5) 3.5 (2.5-4.7) 3.6 (2.6-4.7) 4.3 (3.1-5.8) 0.4 (0.1-2.5) 0 3.2 (1.5-7.0) 5.7 (3.2-10.0) 8.3 (4.8-14.1) 9.2 (5.0-16.3) 0.8 (0.4-1.5) 0.8 (0.4-1.4) 0.9 (0.4-1.7) 0.4 (0.1-2.5) 0.4 (0.1-2.6) 0.5 (0.1-3.7) 1.0 (0.3-4.1) 1.4 (0.4-5.4) 1.8 (0.5-7.1)	14.8 (12.6-17.4) 14.0 (12.1-16.1) 19.1 (16.1-22.3) 0 4.4 (2.2-8.5) 5.7 (2.7-11.4) 24.5 (18.3-31.0) 34.5 (26.3-43.8) 39.3 (29.7-49.9) 3.8 (2.7-5.3) 3.5 (2.6-4.7) - 0.5 (0.1-3.7) 0 4.0 (1.7-9.4) 5.3 (2.7-10.3) 9.7 (5.5-16.8) 6.7 (3.0-14.3) 0.7 (0.3-1.6) 0.7 (0.3-1.3) - 0.5 (0.1-3.7) 0 0 1.3 (0.3-5.2) 1.8 (0.4-6.9) 1.1 (0.2-7.6)	7.1 (4.8-10.4 8.5 (7.0-10.2) 9.4 (6.1-13.8) 1.1 (1.5-7.2) 4.6 (1.7-11.6) 4.8 (1.6-14.1) 9.3 (3.5-22.6) 29.0 (15.6-47.4) 15.0 (4.8-38.4) 2.7 (1.4-5.0) 4.0 (2.9-5.2) - 0 0 1.6 (0.2-10.8) 7.0 (2.2-19.8) 3.2 (0.4-20.3) 20.0 (7.5-43.6) 0.9 (0.3-2.7) 1.1 (0.6-1.9) - 0 1.1 (0.2-7.8) 1.6 (0.2-10.8) 0 0 5.0 (0.7-29.4)	**17**
Maimela 2016[6] [49]	Random Cluster	Black African	NR	Limpopo	Rural	WHO, 1998	≥15	732	OGTT	T2DM 15-24 years 25-34 years 35-44 years 45-54 years 55-64 years >=65 years	12.5 (10.3-15.2) 2.8 (-11.1-6.7) 1.9 (-1.9-5.7) 6.8 (-0.7-14.4) 9.1 (3.0-15.1) 15.7 (7.1-24.3) 18.8 (10.9-26.6)	NR	NR	**11**
Oni 2017 [46]	Convenience, TB clinic	Black African	2013-2015	WC	Peri-urban	WHO 2006, ADA 2013	≥18	852	FPG/OGTT/HbA1c	T2DM HIV negative	11.3 (9.3-13.6) 16.0 (12.2-20.8)	NR	NR	**13**

										HIV positive TB negative TB positive IGR Undiagnosed	8.9 (6.7-11.6) 10.1 (7.6-13.2) 12.6 (9.7-16.1) 57.3 (53.7-60.8) 6.7 (5.1-8.6)			
Zemlin 2018 [41]	Multistage cluster	Coloured	2014-2016	WC	Urban	WHO, 2006	30->60	1507	OGTT/FPG	T2DM Undiagnosed	19.3 (17.3-21.4) 6.4 (5.2-7.7)	NR	NR	**11**
SADHS 2019 [21]	Multistage cluster	All South Africans	2016	National	Urban and Rural	WHO, 2011	>25	4919	HbA1c	T2DM 25-34 years 35-44 years 45-54 years 55-64 years >=65 years	14.9 (13.6-16.3) 4.5 (3.2-6.1) 11.8 (9.3-14.6) 20.8 (17.4-24.5) 28.7 (24.6-33.1) 30.1 (26.1-34.5)	17.3 (15.7-19.1)	11.6 (9.9-13.6)	

[1]Population group was classified according to previously defined apartheid categories of Black African, Coloured, Indian/Asian, White and other, which was introduced into the new birth death notification in 1998 to track health inequalities [32].

[2]Number of participants for case definition

[3]Numbers in age groups not reported, not possible to calculate 95% CI

[4]Study conducted in females only

[5]Study conducted in HIV positive individuals only

[6]Study conducted in HIV negative individuals only

ADA: American Diabetes Association; EC: Eastern Cape; FPG: Fasting plasma glucose; HbA1: Glycated haemoglobin; HIV: Human immunodeficiency virus; IFG: Impaired fasting glucose; IGT: impaired glucose tolerance; IGR: impaired glucose regulation; KZN: KwaZuluNatal; NR: Not reported; OGTT: Oral glucose tolerance test: TB: Tuberculosis; T2DM: type 2 diabetes mellitus; WC: Western Cape; WHO: World Health Organization.

Supplementary Table 4. *Included studies that compared different diagnostic tests*

	Hird 2006 [44]	Oni 2017 [46]		
Diagnostic	**All**	**All**	**No TB**	**TB**
FPG				
T2DM	11.8 (10.1-13.7)	4.1 (3.0-5.7)	3.9 (2.4-6.2)	4.4 (2.8-6.9)
IGR	NR	10.6 (8.6-13.1)	12.5 (9.5-16.1)	8.6 (6.1-12.2)
OGTT				
T2DM	10.3 (8.7-12.2)	3.3 (2.3-4.8)	3.5 (2.1-5.8)	3.1 (1.7-5.3)
IGR	NR	10.6 (8.6-13.0)	4.9 (3.1-7.5)	16.9 (13.3-21.2)
HbA1c				
T2DM	12.9 (11.1-14.9)	8.2 (6.5-10.2)	6.2 (4.3-8.9)	10.2 (7.7-13.6)
IGR	NR	39.5 (36.1-43.0)	34.1 (29.6-38.9)	45.4 (40.3-50.6)

FPG: Fasting plasma glucose; HbA1c: Glycated Haemoglobin; IGR: Impaired glucose regulation; NR: Not reported; OGTT: Oral glucose tolerance test, TB: Tuberculosis; T2DM: type 2 diabetes mellitus.

Supplementary Table 5. *Level of evidence as qualified with GRADE*

Certainty assessment							№ of patients	Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	T2DM_Prevalence	Prevalence Study (%)		
Prevalence of type 2 diabetes (assessed with: The following criteria was used to diagnosed type 2 diabetes: 1. WHO (2006) diagnostic criteria where type 2 diabetes is diagnosed either by a physician, fasting blood glucose concentrations ≥7.0 mmol/L, 2-hour oral glucose tolerance test values ≥11.1 mmol/L or self-reported use of oral diabetes drugs. 2. Glycated haemoglobin ≥6.5% (48 mmol/mol).)										
15	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	17,461 participants	not pooled	⊕◯◯◯ VERY LOW	CRITICAL
Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (assessed with: IGT measured using FPG <7.0 mmol/L and 2-hour OGTT plasma ≥7.8 mmol/L and <11.1 mmol/L; IFG measured using >6.1 mmol/L and < 7.0 mmol/L)										
12	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	IGT: 5783 participants IFG: 6026 participants	not pooled	⊕◯◯◯ VERY LOW	CRITICAL
Undiagnosed type 2 diabetes (assessed with: • T2DM defined as fasting plasma glucose (FPG) ≥7.0 mmol/L, 2-hour oral glucose tolerance test (OGTT) plasma glucose ≥11.1 mmol/L, glycated haemoglobin (HbA1c) ≥6.5% (48 mmol/mol))										
7	observational studies	serious [a]	serious [b]	serious [c]	serious [d]	none	5445 participants	not pooled	⊕◯◯◯ VERY LOW	CRITICAL

Explanations

a. Downgraded by 1 because of limitations in studies design, poor response rate and unclear of risk of bias

b. Downgraded by 1 because of methodological limitations

c. Sampling bias and more studies reporting on female population creating gender bias which negatively affects generalisability

d. Downgraded by 1 because of unclear of risk of bias, and wide confidence intervals

Statistical formula

Formula for calculating confidence intervals in STATA (StataCorp 14.0, College Station, Texas, USA)

cii denominator numerator

INSTRUCTIONS TO AUTHORS

BMJ Open

BMJ Open is an open access journal dedicated exclusively to publishing medical research. The journal aims to provide rapid publication of research across a range of medical disciplines and therapeutic areas, through a continuous publication model. As well as publishing definitive articles, including small and specialist studies, BMJ Open will consider protocols and pilot studies. See here for more information on what we publish. Submissions will only be published after peer review, and reviewers' comments will be published alongside accepted manuscripts.

Research submissions should have a clear, justified research question.

We strongly encourage you to register your study. Prospective registration is mandatory for any clinical trials. Acceptable registries for trials are clinicaltrials.gov along with those listed here. We recommend Prospero for registration of systematic reviews.

All articles should include the following:

- **The article title should include the research question and the study design**. Titles should not declare the results of the study.
- **A structured abstract** (max. 300 words) including all the following where appropriate (please note that for RCTs there is a specific CONSORT extension for abstracts):
    - **objectives:** clear statement of main study aim and major hypothesis/research question
    - **design:** e.g. prospective, randomised, blinded, case control
    - **setting:** level of care e.g. primary, secondary; number of participating centres. Generalise; don't use the name of a specific centre, but give geographical location if important

- **participants:** numbers entering and completing the study; sex and ethnic group if appropriate. Clear definitions of selection, entry and exclusion criteria
- **interventions:** what, how, when and how long (this can be deleted if there were no interventions)
- **primary and secondary outcome measures:** planned (i.e. in the protocol) and those finally measured (if different, explain why) – for quantitative studies only
- **results:** main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks
- **conclusions:** primary conclusions and their implications, suggest areas for further research if appropriate. Do not go beyond the data in the article
- **where applicable, trial registration:** registry and number (for clinical trials and, if available, for observational studies and systematic reviews)

- **An Article Summary, placed after the abstract, consisting of the heading 'Strengths and limitations of this study'**, and containing up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. They should not include the results of the study.
- **The original protocol for the study**, as a supplementary file.
- **A funding statement,** preferably worded as follows. Either: 'This work was supported by [name of funder] grant number [xxx]' or 'This research received no specific grant from any funding agency in the public, commercial or not-for-profit

sectors'. You must ensure that the full, correct details of your funder(s) and any relevant grant numbers are included.

- **A competing interests statement**. See the BMJ Author Hub for details on what to include as competing interests.
- **Articles should list each author's contribution individually at the end**; this section may also include contributors who do not qualify as authors. Please visit the ICMJE website for more information on authorship.
- **Any checklist and flow diagram for the appropriate reporting statement**, e.g. STROBE (see below).
- **A patient consent form:** any article that contains personal medical information about an identifiable living individual requires the patient's explicit consent before we can publish it. We will need the patient to sign our consent form, which requires the patient to have read the article. This form is available in multiple languages.
- **A data sharing statement**, such as: "Technical appendix, statistical code, and dataset available from the Dryad repository, DOI: [include DOI for dataset here].
- **Word count,** we recommend your article does not exceed 4000 words, with up to five figures and tables. This is flexible, but exceeding this will impact upon the paper's 'readability'. Authors are encouraged to submit figures and images in colour – there are no colour charges. We require that you upload your figures as separate files rather than embedding them in the manuscript.
- **Supplementary and raw data** can be placed online alongside the article although we prefer raw data to be made publicly available and linked to in a suitable repository (e.g. Dryad, FigShare). We may request that you separate out some material into supplementary data files to make the main manuscript clearer for readers.

We also recommend, but do not insist, that the discussion section is no longer than five paragraphs and follows this overall structure (you do not need to use these as subheadings): a statement of the principal findings; strengths and weaknesses of the study; strengths and weaknesses in relation to other studies, discussing important differences in results; the meaning of the study: possible explanations and implications for clinicians and policymakers; and unanswered questions and future research.

At upload you will be asked to choose one general subject area that applies to your article – it will be published under this banner on the main table of contents. You will also be asked to select further subject headings to be used for the 'Browse by topic' section, and specific keywords for help with identifying reviewers.

Following the lead of The BMJ and its patient partnership strategy, *BMJ Open* is encouraging active patient involvement in setting the research agenda. As such, we require authors of Research Articles to add a Patient and Public Involvement statement in the Methods section. Please see more details above.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Part A Protocol No.
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	14
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	16
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	14
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	26
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	26
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	19
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	20
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	20
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	22
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	23
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	22,24

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	23
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	24
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	24
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	21,22
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	24
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	25
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	25
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	25
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	25
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	25
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	25

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.** *From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) 2009 checklist: recommended items to address in a systematic review *

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	67
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	69
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	72
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	73
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	75
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	76
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	75
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	75
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	76

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	76
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	77
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	77
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	77
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	78
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	78
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	78
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	79
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	107
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	107
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	84,85,86,87
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	107
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	78

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	88
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	71,89,90
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	90
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	91

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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